Palladium(0)-Catalyzed Coupling of Organozinc Iodide Reagents with Bromopyridines: Synthesis of Selectively Protected Pyridine-Containing Azamacrocycles

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Abstract: The synthesis of azamacrocycles in which the ring nitrogens are regioselectively functionalized is described. An organozinc palladium(0)-catalyzed coupling with an appropriately functionalized bromopyridine generated a key intermediate, which was transformed in two steps to a desired precursor and subjected to an intramolecular N-alkylation to effect a macrocyclization affording selectively protected azamacrocycles **1**−**3**.

Over the past few years, we have reported a novel series of bicyclam structures that exhibit potent and selective inhibition of HIV-1 replication by antagonism of the chemokine receptor CXCR4.[1,2] To identify the pharmacophore necessary for potent anti-HIV activity, a series of unsymmetrical pyridine-containing azamacrocycles were necessary to complete the SAR (Figure 1). However, a review of the literature[3] revealed that methods to synthesize these azamacrocycles with the ability to regioselectively functionalize the macrocyclic ring nitrogens were lacking. This paper reports the first synthesis of selectively protected azamacrocycles **1**−**3** utilizing an organozinc palladium(0)-catalyzed coupling strategy to generate appropriately functionalized precursors, which were then subjected to intramolecular N-alkylation to effect the macrocyclization.

The sequence leading to compounds **1** (R = Ns) and **2** (R = Dep) is shown in Scheme 1. The starting material, (6-bromopyridin-2-yl)acetonitrile **4**, was readily available in 91% yield from 2,6-dibromopyridine using a methodology that we recently developed.[4] Reduction of the cyano group was accomplished using 3 equiv of BH_3·THF in THF at 60 °C to afford the corresponding amine in 72% yield. At this stage, we explored the utility of different protecting groups for the primary amine that could also be used in the macrocyclization reaction. Two protecting groups that we investigated were the diethylphosphoramide[5] and the 2-nitrobenzenesulfonamide;[6] however, on the basis of preliminary experiments that were used to probe the macrocyclization, it was found that the sulfonamide was far superior. As a consequence, to complete the synthesis of compounds **1** and **2**, we used the 2-nitrobenzenesulfonamide **5**, which was prepared in 65% yield.

Generation of the C−C bond at the pyridine C-6 position was explored using the palladium(0)-catalyzed coupling of the bromopyridine **5** with 4-cyanobutylzinc iodide based on the pioneering work by Negishi[7] in the palladium(0)-catalyzed cross-coupling reaction of organozinc iodides.[8] Several different groups[9] have subsequently extended the Negishi cross-coupling method to bromopyridines using organozinc iodides, and several methods[9,10] have been reported in the literature for the generation of organozinc iodides; however, in our hands a modified method described by Walker[9c] proved to be the most reliable. After some experimentation, it was

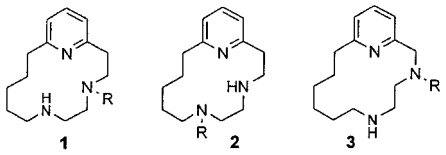
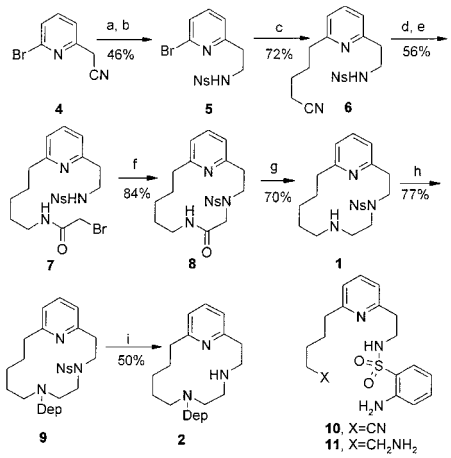


Figure 1. Structures of selectively protected pyridine-containing azamacrocycles.

Scheme 1[a]



[a] Reagents and conditions: (a) BH_3·THF, THF, 60 °C; (b) 2-$NO_2C_6H_4SO_2Cl$ (NsCl), NEt_3, CH_2Cl_2, room temperature; (c) $ZnI(CH_2)_4CN$, $(PPh_3)_2PdCl_2$, THF, 60 °C; (d) BH_3·Me_2S, THF, 60 °C, 4 h; (e) $BrCOCH_2Br$, Na_2CO_3, THF, −15 °C; (f) K_2CO_3, CH_3CN, 60 °C; (g) BH_3·THF, THF, 50 °C; (h) $ClP(O)(OEt)_2$, Et_3N, CH_2Cl_2, room temperature; (i) K_2CO_3, PhSH, DMF, room temperature, 4 h.

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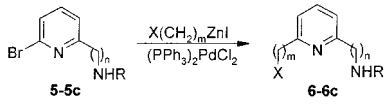
Table 1. Palladium(0)-Catalyzed Coupling of Bromopyridines with Organozinc Iodide Reagents[a]



substrate	R	n	$X(CH_2)_mZnI$	product: yield (%)
5	Ns	2	$CN(CH_2)_4ZnI$	**6**: 72
5a	Dep	2	$CN(CH_2)_4ZnI$	**6a**: 77
5	Ns	2	$BocNH(CH_2)_5ZnI$	no reaction
5b	Dep	1	$CN(CH_2)_5ZnI$	**6b**: 95
5c	Ns	1	$CN(CH_2)_5ZnI$	**6c**: 66

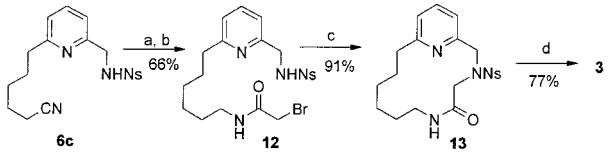
[a] Reactions were carried out in THF at 60 °C using 4 equiv of organozinc iodide reagent.

found that an excess of 4-cyanobutylzinc iodide (4 equiv) was required for complete reaction of the bromopyridine using dichlorobis(triphenylphosphine)palladium(II) as the catalyst. Initial attempts at the coupling reaction using compound **5** resulted in variable yields (40 to 72%) of the desired product **6** with a lower yield being more pronounced on a larger scale. However, use of the diethylphosphoramidate **5a** resulted in a clean reaction affording the desired product **6a** in 77% yield (Table 1), indicating that the outcome of the reaction was influenced by the nitrogen protecting group. In fact, the variable yield with compound **5** was due to the formation of a side product, which was identified as compound **10**, where the nitro group of the sulfonamide was reduced to the corresponding aniline (Scheme 1). We suspected that excess zinc in the reaction medium was responsible for the reduction of the nitro group. Indeed, it was found that filtration of the 4-cyanobutylzinc iodide solution through a 0.45 μm filter prior to being added to the bromide **5** resulted in a consistent yield (65−72%) of the coupled product **6** with no detection of the reduced compound **10**.

Since the ultimate goal was to install a pendant amine function at C-6, the coupling reaction was also attempted using *N*-*tert*-butyloxycarbamoyl-5-pentylaminezinc iodide;[11] however, attempted coupling of this reagent with compound **5** resulted in no reaction (Table 1). Two additional examples that were studied in the palladium(0)-catalyzed coupling reaction were the sulfonamide **5c** and the phosphoramidate **5b**, which were required for the synthesis of **3**. Coupling of compound **5b** with 5-cyanopentylzinc iodide afforded the desired product **6b** in 95% yield, whereas coupling of compound **5c** with the same organozinc reagent afforded the product **6c** in 66% yield.

Reduction of the cyano group of compound **6** was accomplished using 6 equiv of BH_3·Me_2S in THF at 60 °C over 4 h to afford the corresponding amine.[12] In this case, it was important to stop the reaction after 4 h to prevent the formation of byproduct **11** also arising from reduction of the nitro group of the 2-nitrobenzenesulfonamide protecting group (Scheme 1). Reaction of the crude amine with bromoacetyl bromide in THF in the presence of Na_2CO_3 at −15 °C afforded the acetamide **7** in 56% overall yield from **6** (Scheme 1).[13]

Scheme 2[a]



[a] Reagents and conditions: (a) BH_3·Me_2S, THF, 60 °C; (b) $BrCOCH_2Br$, Na_2CO_3, THF, −15 °C; (c) K_2CO_3, CH_3CN, 60 °C; (d) BH_3·THF, THF, 50 °C.

Our initial attempt at effecting the intramolecular macrocyclization utilizing Cs_2CO_3 as a base[14] in DMF under high-dilution conditions[15] at 50 °C resulted in the isolation of the macrocycle **8** in 50% yield as well as a side product in 18% yield, which after characterization was identified as having lost SO_2.[16] By optimizing the reaction conditions, we found that K_2CO_3 in CH_3CN at 60 °C completely shut down the formation of the side product, resulting in the isolation of compound **8** as the sole product in 84% yield. Reduction of the amide function with BH_3·THF complex in THF at 50 °C liberated the secondary amine, affording the selectively protected azamacrocycle **1** (R = Ns) in a 70% yield (Scheme 1). To protect the alternative secondary amine, compound **1** was treated with diethylphosphoryl chloride, affording the diethylphosphoramidate **9** in 77% yield (although any protecting group could have been used). Selective deprotection of the 2-nitrobenzenesulfonamide group was then accomplished using thiophenol in the presence of K_2CO_3 to give compound **2** (R = Dep) in 50% yield. This reaction sequence demonstrates that selective protection of either secondary amine is possible. Both compounds **1** and **2** were subsequently further elaborated and their products assessed for antiviral activity.[17]

The synthesis of macrocycle **3** (R = Ns) was completed starting from nitrile **6c** using a methodology similar to that described for the preparation of **1** (Scheme 2). Reduction of the cyano group of compound **6c** was accomplished using 6 equiv of BH_3·Me_2S in THF at 60 °C over 4 h to afford the corresponding amine (a short reaction time was critical to avoid reduction of the nitro group of the 2-nitrobenzenesulfonamide protecting group). Reaction of the crude amine with bromoacetyl bromide in THF in the presence of Na_2CO_3 at −15 °C afforded the acetamide **12** in 66% overall yield from **6c**. Intramolecular macrocyclization utilizing K_2CO_3 in CH_3CN at 60 °C under high-dilution conditions[15] resulted in the isolation of compound **13** as the sole product in 91% yield.

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Reduction of amide **13** to the corresponding secondary amine with BH_3·THF complex in THF at 50 °C afforded the selectively protected azamacrocycle **3** (R = Ns) in 77% yield (Scheme 2). Compound **3** was also further elaborated and the product assessed for antiviral activity.[17]

In conclusion, the palladium(0)-catalyzed coupling of an organozinc iodide reagent and a bromopyridine followed by intramolecular macrocyclization represents an efficient strategy for the synthesis of selectively functionalized pyridine-containing azamacrocyles.

Experimental Section

^{1}H NMR and ^{13}C NMR spectra were recorded, respectively, at 300 and 75 MHz on a Bruker Avance 300 spectrometer. Mass spectra were obtained on a Bruker Esquire LC Ion Trap spectrometer. Thin-layer chromatography (TLC) was performed on precoated SiO_2 60 F-254 plates (230−400 mesh). THF was dried over sodium and freshly distilled before use. All reactions were performed in oven-dried glassware under a positive pressure of nitrogen. Reaction mixtures were stirred magnetically.

[2-(6-Bromopyridin-2-yl)ethyl]-2-nitrobenzenesulfonamide (5). To 6-bromo pyridyl-2-acetonitrile[4] (7.0 g, 35 mmol) in anhydrous THF (15 mL) at room temperature was added a 1.0 M solution of BH_3·THF (104 mL, 104 mmol) in THF over a period of 20 min. The reaction mixture was warmed to 60 °C and stirred for 18 h. After the reaction mixture was cooled to room temperature, 6 N HCl (30 mL) was added dropwise and the mixture was heated at 70 °C for 2 h and then cooled to room temperature. The resulting clear solution was washed with diethyl ether (3 × 25 mL) and cooled to 0 °C. To the solution was added 10 N NaOH (20 mL), and the aqueous phase was saturated with K_2CO_3. The liberated amine was extracted with chloroform (6 × 20 mL), and the combined organic extracts were dried over a 1:1 mixture of K_2CO_3 and Na_2SO_4. Evaporation of the solvent gave crude 2-(6-bromopyridin-2-yl)ethylamine (5.1 g, 72%): ^{1}H NMR ($CDCl_3$) δ 2.90 (t, J = 6 Hz, 2H), 3.12 (t, J = 6 Hz, 2H), 7.12 (d, J = 9 Hz, 1H), 7.31 (d, J = 9 Hz, 1H), 7.46 (dd, J = 9, 9 Hz, 1H). Using the procedure of Fukuyama,[6] crude 2-(6-bromopyridin-2-yl)ethylamine (5.1 g, 25.36 mmol) gave **5** (6.3 g, 64%) as a white solid after purification (CH_2Cl_2): ^{1}H NMR ($CDCl_3$) δ 3.02 (t, J = 6.3 Hz, 2H), 3.55 (dt, J = 6.3, 6.3 Hz, 2H), 5.93 (br t, 1H), 7.08 (d, J = 7.5 Hz, 1H), 7.26−7.32 (m, 1H), 7.44 (dd, J = 7.5, 7.5 Hz, 1H), 7.74 (m, 2H), 7.84−7.87 (m, 1H), 8.12−8.15 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 37.14, 42.91, 122.92, 125.91, 126.73, 131.34, 133.24, 133.95, 134.08, 134.14, 139.33, 142.24, 159.85; exact mass m/z calcd for $C_{13}H_{12}{}^{81}BrN_3O_4S$ 386.99, found $[M + H]^+$ 387.90.

***N*-(6-Bromopyridin-2-ylmethyl)-2-nitrobenzenesulfonamide (5c).** Using the procedure of Fukuyama,[6] 6-bromopyridin-2-ylmethylamine[18] (3.16 g, 16.90 mmol) gave **5c** (4.6 g, 78%) as a yellow solid after purification (EtOAc−CH_2Cl_2, 30:70): ^{1}H NMR ($CDCl_3$) δ 4.45 (d, J = 6 Hz, 2H), 6.41 (t, J = 6 Hz, 1H), 7.28−7.30 (m, 2H), 7.47 (dd, J = 7.7, 7.7 Hz, 1H), 7.59−7.72 (m, 2H), 7.91 (dd, J = 7.8, 1.5 Hz, 1H), 7.98 (dd, J = 7.8 Hz, 1.5, 1H); ^{13}C NMR ($CDCl_3$) δ 48.52, 121.07, 126.03, 127.54, 130.91, 133.15, 133.95, 134.35, 139.49, 141.96, 148.10, 156.91; exact mass m/z calcd for $C_{12}H_{10}{}^{81}BrN_3O_4S$ 372.98, found $[M + H]^+$ 373.86.

[2-(6-Bromopyridin-2-yl)ethyl]phosphoramidic Acid Diethyl Ester (5a). Using the procedure of Bridger et al.,[2f] 2-(6-bromopyridin-2-yl)ethylamine (705 mg, 3.51 mmol) gave **5a** (1.08 g, 92%) as a white foam after purification (MeOH−CH_2Cl_2, 5:95): ^{1}H NMR ($CDCl_3$) δ 1.32 (t, J = 7.1 Hz, 6H), 2.80−2.92 (m, 1H), 2.95 (t, J = 6.6 Hz, 2H), 3.29−3.39 (m, 2H), 3.94−4.12 (m, 4H), 7.14 (d, J = 8.9 Hz, 1H), 7.35 (d, J = 9.1 Hz, 1H), 7.47 (dd, J = 9.1, 9.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 16.62 ($^3J_{PC}$ = 6.9 Hz), 39.53 ($^2J_{PC}$ = 5.2 Hz), 40.91, 62.70 ($^2J_{PC}$ = 5.1 Hz), 122.92, 126.33, 139.43, 142.15, 161.10; exact mass m/z calcd for $C_{11}H_{18}{}^{81}BrN_2O_3P$ 338.10, found $[M + Na]^+$ 361.10.

***N*-(6-Bromopyridin-2-ylmethyl)phosphoramidic Acid Diethyl Ester (5b).** Using the procedure of Bridger et al.,[2f] 6-bromopyridine-2-ylmethylamine[18] (123 mg, 0.66 mmol) gave **5b** (180 mg, 85%) as a white foam after purification (EtOAc−CH_2Cl_2, 30:70): ^{1}H NMR ($CDCl_3$) δ 1.29 (dt, J = 6.9, 0.6 Hz, 6H), 3.55−3.60 (m, 1H), 3.97−4.15 (m, 4H), 4.20 (dd, J = 10.4, 6.8 Hz, 2H), 7.30 (d, J = 7.5 Hz, 1H), 7.38 (d, J = 7.5 Hz, 1H), 7.50−7.56 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 16.52 ($^3J_{PC}$ = 7.0 Hz), 46.35, 62.90 ($^2J_{PC}$ = 5.1 Hz), 120.57, 127.02, 139.40, 142.01, 160.22; exact mass m/z calcd for $C_{10}H_{16}{}^{81}BrN_2O_3P$ 324.13, found $[M + Na]^+$ 347.00.

General Procedure for the Pd(0)-Catalyzed Coupling of Bromopyridines with Organozinc Iodide Reagents. To a round-bottom flask containing Zn dust (1.30 g, 20.0 mmol) was added dibromoethane (305.2 mg, 1.62 mmol), and the resulting mixture was warmed to 60 °C and then allowed to cool for 1 min. This heating−cooling process was repeated three more times, and then the flask was allowed to cool for an additional 3 min. Trimethylsilyl chloride (26.5 mg, 0.24 mmol) in THF (20 mL) was added; the resulting mixture was warmed to 60 °C, and a solution of alkyl iodide (6.5 mmol) in THF (1 mL) was added. The mixture was stirred at 60 °C until all the alkyl iodide had been consumed (ca. 4 h, TLC control). The resulting solution of alkylzinc iodide was transferred by a syringe fitted with a 0.45 μm filter to a second flask charged with the bromopyridine **5**−**5c** (1.3 mmol) and $(Ph_3P)_2PdCl_2$ (45 mg, 0.06 mmol). The resulting mixture was stirred for 18 h at 60 °C under N_2, cooled to room temperature, and quenched with saturated aqueous NH_4Cl solution (5 mL). The resulting mixture was stirred for 20 min at room temperature and diluted with ethyl acetate (200 mL), and the organic phase was washed with saturated aqueous NH_4Cl (50 mL) and brine (50 mL) and dried over Na_2SO_4. The organic phase was concentrated, and the crude material was purified by flash column chromatography on silica gel using ethyl acetate−CH_2Cl_2 or MeOH−CH_2Cl_2 as the eluant.

{2-[6-(4-Cyanobutyl)pyridin-2-yl]ethyl}-2-nitrobenzenesulfonamide (6). Bromide **5** (503 mg, 1.3 mmol) gave **6** (363 mg, 72%) as a light yellow oil after purification (EtOAc−CH_2Cl_2, 5:95): ^{1}H NMR ($CDCl_3$) δ 1.69−1.78 (m, 2H), 1.83−1.93 (m, 2H), 2.41 (t, J = 7.1 Hz, 2H), 2.83 (t, J = 7.5 Hz, 2H), 3.00 (t, J = 5.9 Hz, 2H), 3.54 (dt, J = 5.7, 5.7 Hz, 2H), 6.86 (d, J = 12.3 Hz, 1H), 7.00 (d, J = 8.1 Hz, 1H), 7.08 (br s, 1H), 7.50 (dd, J = 7.5, 7.5 Hz, 1H), 7.71−7.76 (m, 2H), 7.83−7.86 (m, 1H), 8.14−8.18 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 17.40, 25.42, 29.07, 36.43, 37.53, 42.98, 120.20, 121.18, 121.21, 125.66, 131.34, 133.10, 133.71, 134.66, 137.47, 148.39, 158.61, 161.27; exact mass m/z calcd for $C_{18}H_{20}N_4O_4S$ 388.12, found $[M + H]^+$ 389.01.

{2-[6-(5-Cyanopentyl)pyridin-2-yl]methyl}-2-nitrobenzenesulfonamide (6c). Bromide **5c** (594 mg, 1.60 mmol) gave **6c** (407 mg, 66%) as a yellow oil after purification (EtOAc−CH_2Cl_2, 5:95): ^{1}H NMR ($CDCl_3$) δ 1.43−1.53 (m, 2H), 1.65−1.78 (m, 4H), 2.36 (t, J = 7.1 Hz, 2H), 2.68 (t, J = 7.7 Hz, 2H), 4.39 (d, J = 6.0 Hz, 2H), 6.85 (s, 1H), 6.99 (d, J = 12.6 Hz, 1H), 7.02 (d, J = 12.9 Hz, 1H), 7.50 (dd, J = 7.7, 7.7 Hz, 1H), 7.65−7.72 (m, 2H), 7.86−7.89 (m, 1H), 8.08−8.13 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 17.38, 25.51, 28.53, 28.63, 37.83, 48.32, 119.40, 120.12, 122.12, 125.77, 131.43, 133.02, 133.77, 134.18, 137.46, 148.35, 153.88, 161.67; exact mass m/z calcd for $C_{18}H_{20}N_4O_4S$ 388.12, found $[M + H]^+$ 388.99.

2-Bromo-*N*-(5-{6-[2-(2-nitrobenzenesulfonylamino)ethyl]pyridin-2-yl}pentyl) Acetamide (7). To a solution of **6** (410 mg, 1.05 mmol) in anhydrous THF (15 mL) at room temperature was added neat BH_3·Me_2S (0.6 mL, 6.0 mmol) over a period of 2 min. The reaction mixture was warmed to 60 °C, and stirring was continued for another 4 h. After the reaction mixture was cooled to room temperature, 6 N HCl (3.3 mL) was carefully added dropwise, resulting in the evolution of H_2 (g). The mixture was heated to 70 °C for 2 h, resulting in a clear solution. Water (10 mL) was added, and the aqueous solution was washed with diethyl ether (3 × 25 mL) and cooled to 0 °C. To the solution was added 10 N NaOH (2.3 mL), and the aqueous phase was saturated with solid K_2CO_3. The liberated amine was extracted with chloroform (6 × 20 mL), and the combined organic extracts were dried over a 1:1 mixture of K_2CO_3 and Na_2SO_4. Evaporation of the solvent gave the crude amine (320 mg, 77%), which was used directly in the next step: ^{1}H NMR ($CDCl_3$) δ 1.38−1.50 (m, 4H), 1.68−1.73 (m, 2H), 2.68−2.80 (m, 4H), 2.97 (t, J = 5.9 Hz, 2H), 3.54 (t, J = 5.9 Hz, 2H), 4.95 (s, 1H), 6.83 (d, J = 7.5 Hz, 1H), 6.96 (d, J = 7.5 Hz, 1H), 7.46 (dd, J = 7.8, 7.8 Hz, 1H), 7.69−7.72 (m, 2H), 7.80−7.81 (m, 1H), 8.13−8.16 (m, 1H). To a

(18) Chuang, C.-L.; Dos Santos, O.; Xu, X.; Canary, J. W. *Inorg. Chem.* **1997**, *36*, 1967−1972.

stirred solution of crude *N*-{2-[6-(5-aminopentyl)pyridin-2-yl]-ethyl}-2-nitrobenzenesulfonamide (320 mg, 0.82 mmol) and anhydrous Na_2CO_3 (460 mg, 4.34 mmol) in anhydrous THF (15 mL) at −15 °C was added dropwise a solution of bromoacetyl bromide (247 mg, 1.23 mmol) in THF (1 mL). The reaction mixture was stirred at −15 °C for an additional 2 h, diluted with ethyl acetate (200 mL), and warmed to room temperature. The resulting organic solution was washed with saturated aqueous $NaHCO_3$ (60 mL) and brine (60 mL), dried over Na_2SO_4, and concentrated. Purification of the crude material by flash column chromatography on silica gel (2 × 20 cm) using ethyl acetate−CH_2Cl_2 (40:60) gave **7** (311 mg, 73%) as a white foam: ^{1}H NMR ($CDCl_3$) δ 1.36−1.43 (m, 2H), 1.56−1.66 (m, 2H), 1.69−1.79 (m, 2H), 2.80 (t, J = 7.5 Hz, 2H), 2.98 (t, J = 5.7 Hz, 2H), 3.30 (td, J = 6.9, 6.9 Hz, 2H), 3.54 (td, J = 5.4, 5.4 Hz, 2H), 3.86 (s, 2H), 6.56 (br s, 1H), 6.87 (d, J = 7.5 Hz, 1H), 6.99 (d, J = 7.8 Hz, 1H), 7.26 (br s, overlapped with $CHCl_3$, 1H), 7.47 (d, J = 7.7 Hz, 1H), 7.68−7.76 (m, 2H), 7.83−7.86 (m, 1H), 8.15−8.18 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 26.31, 28.99, 29.32, 29.40, 35.96, 37.86, 40.09, 42.66, 120.53, 120.80, 125.22, 130.96, 132.64, 133.27, 134.37, 136.98, 148.20, 158.03, 161.90, 165.48; exact mass *m*/*z* calcd for $C_{20}H_{25}{}^{81}BrN_4SO_5$ 514.09, found $[M + H]^+$ 515.02.

4-(2-Nitrobenzenesulfonyl)-4,7,17-triazabicyclo[11.3.1]-heptadeca-1(17),13,15-trien-6-one (8). A solution of **7** (439 mg, 0.86 mmol) and K_2CO_3 (604 mg, 4.3 mmol) in anhydrous CH_3-CN (1000 mL) was stirred for 18 h at 60 °C. The reaction mixture was then cooled to room temperature and concentrated. The residue was diluted with ethyl acetate (400 mL), and the organic solution was washed with saturated aqueous $NaHCO_3$ (100 mL) and brine (100 mL) and dried over Na_2SO_4. Concentration of the organic fractions and purification of the crude material by flash column chromatography on silica gel (2 × 20 cm) using ethyl acetate−CH_2Cl_2 (50:50) gave **8** (310 mg, 84%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 1.53 (q, J = 6.9 Hz, 2H), 1.62−1.70 (m, 2H), 1.82−1.90 (m, 2H), 2.89−2.93 (m, 2H), 3.02−3.05 (m, 2H), 3.47 (dt, J = 5.4, 5.4 Hz, 2H), 3.77−3.81 (m, 2H), 3.83 (s, 2H), 7.06 (dd, J = 7.8, 7.8 Hz, 2H), 7.56−7.63 (m, 2H), 7.68−7.73 (m, 2H), 8.02−8.05 (m, 1H), 8.59 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 24.09, 26.02, 26.77, 35.51, 37.14, 39.22, 53.10, 53.43, 121.29, 122.33, 124.69, 131.90, 132.09 (2C), 134.23, 137.66, 148.67, 157.93, 161.53, 168.38; exact mass *m*/*z* calcd for $C_{20}H_{24}N_4O_5S$ 432.15, found $[M + H]^+$ 433.07.

4-(2-Nitrobenzenesulfonyl)-4,7,17-triazabicyclo[11.3.1]-heptadeca-1(17),13,15-triene (1). Following the general procedure for the synthesis of compound **5**, **8** (127 mg, 0.29 mmol) gave after purification of the crude material by column chromatography over silica gel (1.0 × 20 cm) using MeOH−NH_4-OH−CH_2Cl_2 (3:3:94) **1** (90 mg, 70%) as a light yellow oil as well as some recovered **8** (21 mg, 7.9%): ^{1}H NMR ($CDCl_3$) δ 1.32−1.39 (m, 2H), 1.47−1.54 (m, 2H), 1.56 (1H, overlap with H_2O), 1.85−1.91 (m, 2H), 2.66−2.73 (m, 4H), 2.87 (t, J = 6.0 Hz, 2H), 3.07 (t, J = 6.3 Hz, 2H), 3.18 (t, J = 6.5 Hz, 2H), 3.88 (t, J = 6.0 Hz, 2H), 7.01 (d, J = 7.5 Hz, 2H), 7.50 (dd, J = 7.8, 7.8 Hz, 1H), 7.60−7.69 (m, 3H), 7.97−8.01 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 23.70, 26.32, 27.40, 36.03, 38.20, 47.72, 47.76, 49.29, 49.47, 121.43, 121.86, 124.47, 131.16, 131.96, 133.36, 133.87, 137.13, 148.65, 157.91, 161.66; exact mass *m*/*z* calcd for $C_{20}H_{26}N_4O_4S$ 418.14, found $[M + H]^+$ 419.12.

[4-(2-Nitrobenzenesulfonyl)-4,7,17-triazabicyclo[11.3.1]-heptadeca-1(17),13,15-trien-7-yl]phosphoramidic Acid Diethyl Ester (9). Using the procedure of Bridger et al.,[2f] amine **1** (151 g, 0.36 mmol) gave **9** (148 mg, 77%) as a white foam after purification (EtOAc−CH_2Cl_2, 30:70): ^{1}H NMR ($CDCl_3$) δ 1.19 (t, J = 7.1 Hz, 8H), 1.19−1.21 (m, 2H), 1.35−1.42 (m, 2H), 1.82−1.91 (m, 2H), 2.32−2.42 (m, 2H), 2.79−2.90 (m, 6H), 3.01−3.05 (m, 2H), 3.74−3.92 (m, 6H), 7.02 (dd, J = 12.3, 7.8 Hz, 2H), 7.51 (dd, J = 7.5, 7.5 Hz, 1H), 7.58−7.62 (m, 1H), 7.68 (dd, J = 7.1, 7.1 Hz, 2H), 8.03−8.06 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 16.47 ($^3J_{PC}$ = 7.2 Hz), 24.44, 27.68, 28.16 ($^3J_{PC}$ = 2.9 Hz), 37.20, 39.77, 45.18 ($^2J_{PC}$ = 3.7 Hz), 47.83 ($^3J_{PC}$ = 4.3 Hz), 49.16, 49.49, 62.47 ($^2J_{PC}$ = 5.7 Hz), 121.84, 122.68, 124.34, 131.63, 132.04, 133.62, 133.86, 137.30, 148.51, 158.46, 162.48; exact mass *m*/*z* calcd for $C_{24}H_{35}N_4O_7PS$ 554.20, found $[M + H]^+$ 555.21.

(4,7,17-Triazabicyclo[11.3.1]heptadeca-1(17),13,15-trien-7-yl)phosphoramidic Acid Diethyl Ester (2). To a stirred solution of **9** (67 mg, 0.12 mmol) and anhydrous K_2CO_3 (134 mg, 0.97 mmol) in anhydrous DMF (1.5 mL) was added dropwise neat thiophenol (75 mg, 0.68 mmol). The reaction mixture was stirred at room temperature for 4 h and then concentrated. The residue was diluted with ethyl acetate (100 mL), and the resulting solid was filtered by being passed though a short Celite column. Evaporation of the solvent and purification of the crude material by radial chromatography (silica gel, 1 mm plate) using MeOH−NH_4OH−CH_2Cl_2 (3:3:94) as the eluant gave **2** (22.6 mg, 50%) as a light yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.15 (t, J = 7.1 Hz, 6H), 1.20−1.28 (m, 2H), 1.43−1.97 (m, 5H), 2.70−2.74 (m, 2H), 2.78−2.81 (m, 2H), 2.84−3.25 (m, 8H), 3.62−3.87 (m, 4H), 6.96 (m, 2H), 7.48 (dd, J = 12, 12 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 16.47 ($^3J_{PC}$ = 7.1 Hz), 25.38, 28.33, 30.82, 36.76, 37.57, 48.48, 49.85 ($^2J_{PC}$ = 3.4 Hz), 50.01 ($^2J_{PC}$ = 3.4 Hz), 50.13, 62.19 ($^2J_{PC}$ = 5.7 Hz), 121.21, 121.25, 136.80, 159.30, 161.80; exact mass *m*/*z* calcd for $C_{18}H_{32}N_3O_3P$ 369.22, found $[M + H]^+$ 370.10.

2-Bromo-*N*-(5-{6-[2-(2-nitrobenzenesulfonylamino)methyl]pyridin-2-yl}hexyl) Acetamide (12). Following the procedure for the synthesis of compound **7**, nitrile **6c** (273 mg, 0.70 mmol), after purification of the crude material by flash column chromatography on silica gel (2 × 20 cm) using ethyl acetate−CH_2Cl_2 (20:80) gave **12** (243 mg, 67%) as a white foam: ^{1}H NMR ($CDCl_3$) δ 1.34−1.37 (m, 4H), 1.59 (m, 2H), 1.62−1.69 (m, 2H), 2.63 (t, J = 7.7 Hz, 2H), 3.25 (dt, J = 6.6, 6.6 Hz, 2H), 5.89 (s, 2H), 4.38 (d, J = 5.1 Hz, 2H), 6.51 (b, 1H), 6.90 (b, 1H), 6.96 (d, J = 12.0 Hz, 1H), 6.98 (d, J = 12.3 Hz, 1H), 7.48 (dd, J = 7.7, 7.7 Hz, 1H), 7.64−7.71 (m, 2H), 7.86−7.89 (m, 1H), 8.09−8.11 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 26.88, 29.10, 29.44, 29.73, 38.12, 40.58, 48.36, 119.27, 122.11, 125.77, 131.40, 133.05, 133.81, 134.15, 137.40, 148.33, 153.73, 162.27, 165.84; exact mass *m*/*z* calcd for $C_{20}H_{25}81BrN_4O_5S$ 514.09, found $[M + H]^+$ 515.03.

3-(2-Nitrobenzenesulfonyl)-3,6,17-triazabicyclo[11.3.1]-heptadeca-1(17),13,15-trien-5-one (13). Following the procedure for the synthesis of compound **8**, acetamide **12** (243 mg, 0.47 mmol), after purification of the crude material by flash column chromatography on silica gel (1.5 × 20 cm) using ethyl acetate−CH_2Cl_2 (40:60), gave **13** (186 mg, 91%) as a white foam: ^{1}H NMR ($CDCl_3$) δ 1.17−1.24 (m, 2H), 1.36−1.44 (m, 2H), 1.47−1.52 (m, 2H), 1.70−1.78 (m, 2H), 2.55−2.60 (m, 2H), 3.23 (dt, J = 5.4, 5.5 Hz, 2H), 4.11 (s, 2H), 4.59 (s, 2H), 7.03 (d, J = 7.8 Hz, 1H), 7.11 (J = 7.3 Hz, 1H), 7.48−7.51 (m, 1H), 7.57−7.73 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 23.33, 24.53, 27.17, 28.01, 35.73, 37.22, 53.71, 56.29, 121.10, 123.17, 124.70, 131.88, 131.93, 133.17, 134.12, 137.77, 148.45, 154.10, 162.94, 167.71; exact mass *m*/*z* calcd for $C_{20}H_{24}N_4O_5S$ 432.15, found $[M + H]^+$ 433.05.

3-(2-Nitrobenzenesulfonyl)-3,6,17-triazabicyclo[11.3.1]-heptadeca-1(17),13,15-triene (3). Following the procedure for the synthesis of compound **1**, amide **13** (265 mg, 0.61 mmol), after purification of the crude material by radial chromatography (silica gel, 2 mm plate) using MeOH−NH_4OH−CH_2Cl_2 (3:3:94) as the eluant, gave **3** (198 mg, 77%) as a light yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.11−1.20 (m, 2H), 1.30−1.34 (m, 2H), 1.39−1.48 (m, 2H), 1.82−1.91 (m, 2H), 2.31 (t, J = 6.2 Hz, 2H), 2.58 (t, J = 6.2 Hz, 2H), 2.83−2.87 (m, 2H), 3.38 (t, J = 6.2 Hz, 2H), 4.63 (s, 2H), 7.08 (d, J = 7.5 Hz, 1H), 7.26 (overlapped with $CHCl_3$, 1H), 7.58−7.66 (m, 2H), 7.67−7.73 (m, 2H), 8.14−8.17 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 23.78, 24.81, 27.53, 27.57, 36.37, 47.12, 48.00, 49.53, 54.91, 120.60, 122.85, 124.50, 131.61, 131.93, 133.43, 133.89, 137.53, 148.69, 156.12, 162.24; exact mass *m*/*z* calcd for $C_{20}H_{26}N_4O_4S$ 418.17, found $[M + H]^+$ 419.09.

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Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra of compounds **1**−**9** and **12**−**13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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