

HETEROCYCLES, Vol. 70, 2006, pp. 557 - 570. © The Japan Institute of Heterocyclic Chemistry
Received, 20th July, 2006, Accepted, 31st August, 2006, Published online, 1st September, 2006. COM-06-S(W)16

EVALUATION OF STRATEGIES FOR THE SYNTHESIS OF THE GUANIDINE HEMIAMINAL PORTION OF PALAU'AMINE†

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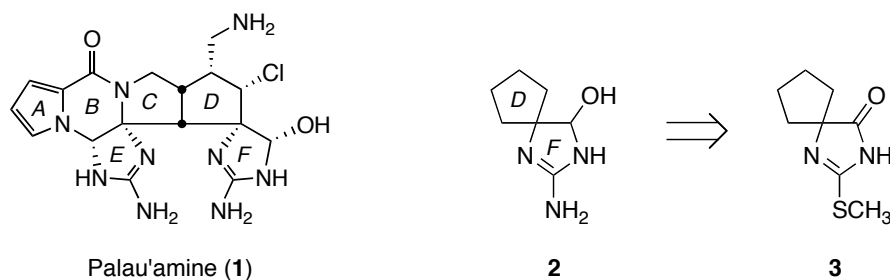
Abstract – Potential methods for the generation of the guanidine hemiaminal functionality of palau'amine (**1**) from a spirocyclic thiohydantoin precursor are examined using a spirobicyclic model system, culminating in the identification of an efficient means of effecting this transformation.

†In recognition of his many contributions to organic synthesis and heterocyclic chemistry, this contribution is dedicated to a close friend, Steven Weinreb, on the occasion of his 65th birthday.

INTRODUCTION

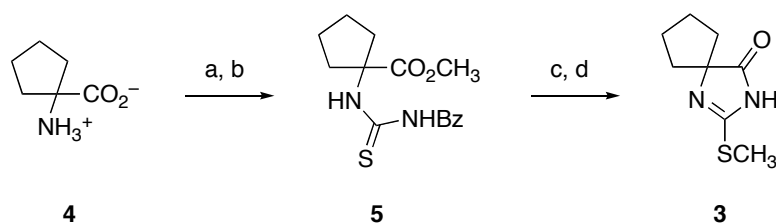
The architecturally intricate marine natural product palau'amine (**1**) was first isolated from *Stylotella aurantium* in 1991.¹ Biochemical assays have since revealed palau'amine to possess exceptional immunosuppressive activity (IC₅₀ < 18 ng/mL, mixed lymphocyte reaction), identifying it as an important target for total synthesis. Despite considerable synthetic investigation in the intervening years,² palau'amine (**1**) has yet to succumb to total synthesis. During efforts toward the total synthesis of **1**, we required methods for constructing the spiro guanidine hemiaminal (2-aminoimidazolin-5-ol) functionality of the palau'amine F-ring. Several methods for the preparation of closely related heterocycles have been reported previously: (1) rearrangement of 2-(hydroxylamino)imidazoles,^{3a} (2) condensation of guanidine salts with glyoxal^{3b} or glyoxylate hemiacetals,⁴ and (3) oxidation of 2-aminoimidazoles in the presence of an alcohol.⁵ However, none of these methods appeared readily compatible with our proposed synthetic approach to **1**, wherein an *S*-methylated thiohydantoin (cf., **3**) was envisioned as a precursor of the spirobicyclic guanidine hemiaminal functionality. To evaluate alternative approaches for the synthesis

of the spiro 2-aminoimidazolin-5-ol portion of **1**, we examined a range of methods for the conversion of 1,3-diaza-2-(methylthio)spiro[4.4]non-1-en-4-one (**3**), an analog of the D/F-ring system of **1**, to the corresponding spirobicyclic guanidine hemiaminal (**2**) (2-amino-1,3-diazaspiro[4.4]non-1-en-4-ol).



RESULTS AND DISCUSSION

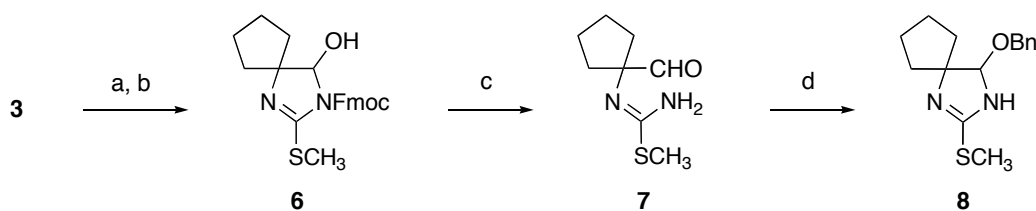
We commenced these studies by preparing *S*-methylated thiohydantoin (**3**) from commercially available 1-aminocyclopentane carboxylic acid (**4**) (Scheme 1). This process was initiated by Fischer esterification of **4**, followed by condensation of the resulting α -amino ester with benzoyl isothiocyanate, affording thiourea (**5**). Exposure of **5** to methanolic potassium carbonate led to cyclization to the corresponding thiohydantoin, followed by cleavage of the *N*-benzoyl group. *S*-Methylation of the resulting spirobicyclic thiohydantoin⁶ then furnished diazaspiro[4.4]nonenone (**3**).



Scheme 1. Reagents and conditions: (a) AcCl , CH_3OH , $0 \rightarrow 40^\circ\text{C}$; (b) BzNCS , Et_3N , CH_2Cl_2 , 23°C ; (c) K_2CO_3 , CH_3OH , 23°C (85%; 3 steps); (d) CH_3I , NaOH , CH_3OH , H_2O , 23°C (82%).

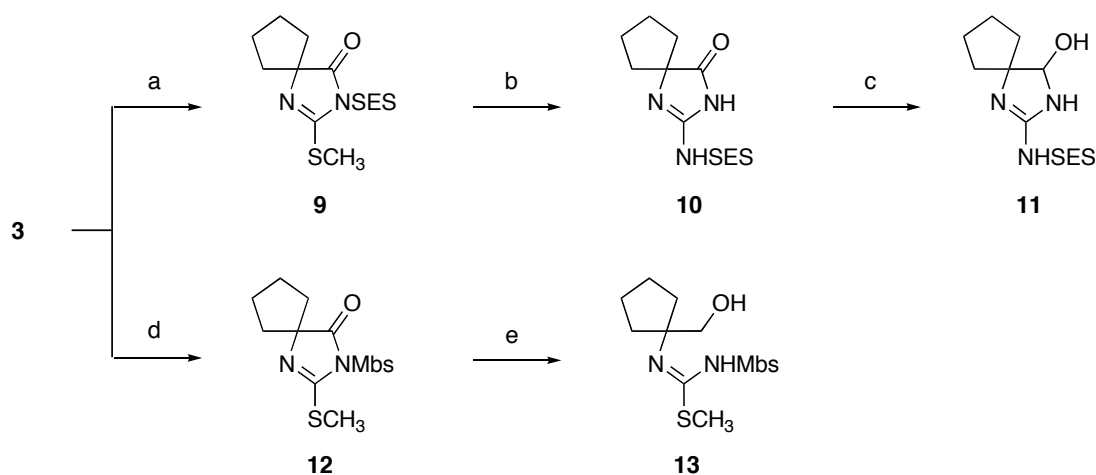
Our initial studies toward the conversion of **3** to guanidine hemiaminal (**2**) were guided by the goal of delaying guanidine installation as long as possible, as such a strategy promised to simplify the chromatographic purification of intermediates in a subsequent synthesis of **1**. We therefore initially examined reduction of the carbonyl group of **3** to the corresponding hemiaminal prior to introduction of the final nitrogen. We achieved this goal by adding an *N*-9-fluorenylmethoxycarbonyl (*N*-Fmoc) protective group to thiohydantoin derivative (**3**), thereby potentiating borohydride-mediated reduction of **3** to *N*-Fmoc 1,3-diaza-2-(methylthio)spiro[4.4]non-1-en-4-ol (**6**) (Scheme 2).⁷ In an attempt to generate the parent heterocycle, the *N*-Fmoc group was then cleaved from **6** by exposure to an excess of

1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) at room temperature. However, the product formed in this reaction, **7**, was found to exist exclusively as the ring-opened tautomer in chloroform, methanol, and dimethyl sulfoxide. Ring formation could be promoted by incubating aldehyde (**7**) with benzyl alcohol and 4Å molecular sieves in the presence of 10-camphorsulfonic acid (CSA), allowing for the isolation of 4-benzyloxy-1,3-diaza-2-(methylthio)spiro[4.4]non-1-ene (**8**). Unfortunately, attempts to convert *O*-benzyl hemiaminal (**8**) to the corresponding spirobicyclic guanidine hemiaminal were unsuccessful, as exposure of **8** to ethanolic ammonia at room temperature only resulted in substitution of ammonia or ethanol for the benzyloxy group. Prolonged heating of these substitution products with ethanolic ammonia triggered rearrangement of the products to 2-methylthio-4,5,6,7-tetrahydrobenzimidazole,⁸ and attempts to facilitate the aminolysis of **8** by converting **8** to the corresponding sulfone⁹ were likewise unsuccessful and led only to substrate decomposition.



Scheme 2. Reagents and conditions: (a) FmocCl, NaH, THF, 0 °C (92%); (b) NaBH₄, CH₃OH, 0 °C (86%); (c) DBU, CH₂Cl₂, 23 °C (85%); (d) BnOH, CSA, 4Å mol. sieves, CH₂Cl₂, 23 °C (55%).

The difficulties encountered in converting *O*-benzyl hemiaminal (**8**) to the corresponding guanidine, engendered by the acid- and base-lability of the aminal portion of **8**, led us to pursue an alternative strategy for the synthesis of aminodiazaspiro[4.4]nonenol (**2**) in which generation of the hemiaminal function of **2** would be deferred until after guanidine installation. As the *N*-substitution of pseudothioureas with electron-withdrawing protective groups has frequently been employed to facilitate pseudothiurea aminolysis,¹⁰ we next examined the aminolysis of *N*-2-(trimethylsilyl)ethylsulfonyl-protected (*N*-SES)¹¹ spirobicyclic (methylthio)imidazolone (**9**), which was prepared in one step from *S*-methylated thiohydantoin (**3**) (Scheme 3). Gratifyingly, exposure of **9** to ammonia-saturated methanol at 23 °C rapidly and cleanly led to the formation of the corresponding spiro glycyamidine (**10**).¹² Reduction of glycyamidine (**10**) to the corresponding hemiaminal proved more difficult. This reduction was ultimately accomplished through the use of excess diisobutylaluminum hydride (DIBAL), affording hemiaminal (**11**) in moderate yield (47%).^{13,14} Our inability to cleave the *N*-SES protective group from this product ultimately proved the undoing of this synthetic route, however, as treatment of **11** with aqueous HF or HF•pyridine resulted in no detectible reaction.¹⁵

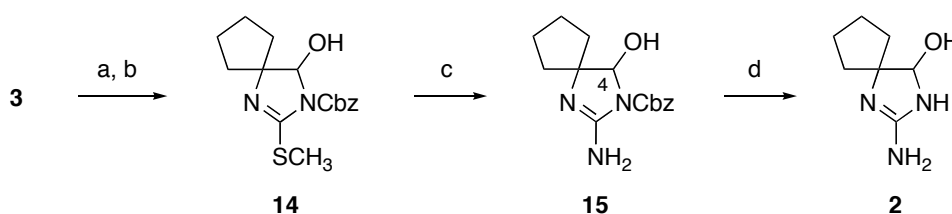


Scheme 3. Reagents and conditions: (a) SESCOI, NaH, THF, 0 °C (66%); (b) NH₃, CH₃OH, 0→23 °C (92%); (c) DIBAL, THF, -78→0 °C (47%); (d) MbsCl, NaH, THF, 0 °C (89%); (e) NaBH₄, CH₃OH, 0 °C (100%). (SES = 2-(trimethylsilyl)ethylsulfonyl; Mbs = 4-methoxybenzenesulfonyl.)

The facility of the aminolysis of *N*-sulfonyl pseudothiurea (**9**) prompted renewed investigation of a synthetic sequence involving initial generation of the hemiaminal function of **2**, followed by guanidine installation. Reduction of an *N*-sulfonyl-protected intermediate such as **12** to the corresponding hemiaminal would be expected to proceed under considerably milder conditions than those required for reduction of glycocyamidine (**10**).¹³ It was hoped that aminolysis of the resulting *N*-sulfonyl-pseudothiurea hemiaminal might, like the aminolysis of *N*-sulfonyl pseudothiurea (**9**), prove rapid, allowing efficient access to guanidine hemiaminals related to **11**. Unfortunately, facile over-reduction of the Mbs-protected derivative (**12**) to the ring-opened primary alcohol (**13**) ultimately thwarted this synthetic plan.

As an *N*-Fmoc congener of **12** had demonstrated excellent kinetic stability toward over-reduction (Scheme 2), we next considered a related strategy in which an *N*-acyloxy group would facilitate late-stage conversion of a pseudothiurea fragment to the corresponding guanidine (Scheme 4).¹⁶ To examine this possibility, *N*-Cbz-protected 1,3-diaza-2-(methylthio)spiro[4.4]non-1-en-4-ol (**14**) was prepared in high yield from *S*-methylated thiohydantoin (**3**) by sequential *N*-alkoxyacylation (CbzCl, NaH) and reduction (NaBH₄, CH₃OH, 0 °C).^{17,18} The products obtained upon subsequent aminolysis of pseudothiurea (**14**) proved to be remarkably solvent dependant. For example, treatment of **14** with methanolic ammonia at 80 °C in a sealed tube for 22 h led exclusively to cleavage of the carbamate, followed by rearrangement of the resulting hydroxyimidazoline to 2-methylthio-4,5,6,7-tetrahydrobenzimidazole. However, in non-protic solvents (e.g., acetonitrile, *N,N*-dimethylformamide, or tetrahydrofuran), carbamate cleavage was suppressed, allowing aminolysis to proceed in good yield at 80 °C to generate *N*-Cbz-protected 2-amino-1,3-diazaspiro[4.4]non-1-en-4-ol (**15**). Furthermore, in contrast to the results observed with

hemiaminal (**8**), only a limited amount of the C4-amino analog of **15** was detected during this reaction, indicating limited ammonia exchange into the hemiaminal under these conditions.¹⁹ Efficient access to guanidine hemiaminal (**15**) set the stage for a final deprotection reaction: hydrogenolytic cleavage of the *N*-Cbz protective group of **15** proved straightforward (10% Pd/C, 1 atm H₂, AcOH, THF), delivering 2-amino-1,3-diazaspiro[4.4]non-1-en-4-ol (**2**) in high yield (73%).



Scheme 4. Reagents and conditions: (a) CbzCl, NaH, THF, 0 °C (95%); (b) NaBH₄, CH₃OH, 0 °C (88%); (c) NH₃, THF, 80 °C, sealed tube (68%); (d) 10% Pd/C, H₂ (1 atm), THF, AcOH, 23 °C (73%).

In this note, we have reported the identification of a method for the conversion of *S*-methyl thiohydantoin (**3**) to the corresponding guanidine hemiaminal (**2**), establishing a potential method for the generation of the guanidine hemiaminal portion of palau'amine (**1**) from a thiohydantoin precursor. These studies have additionally identified several key features of the chemistry of 1,3-diaza-2-(methylthio)spiro[4.4]non-1-en-4-ols, including: (1) the influence of *N*-protecting groups on the position of the tautomeric equilibrium between ring-open and ring-closed forms, (2) the lability of these compounds and their corresponding ether derivatives (e.g., **8**) toward acid- and base-mediated exchange with external nucleophiles at C4 and toward rearrangement to 2-methylthio-4,5,6,7-tetrahydrobenzimidazole, and (3) the role of electron-withdrawing *N*-protective groups in facilitating the aminolysis of pseudothiourea hemiaminals. This knowledge is currently being applied in efforts toward the total synthesis of palau'amine (**1**).

EXPERIMENTAL

Reactions were performed in oven-dried glassware fitted with rubber septa under a positive pressure of argon. Dichloromethane and tetrahydrofuran were dried by passage through a bed of activated alumina.²⁰ Commercial reagents were used as received. Organic solutions were concentrated by rotary evaporation (1 Torr, 23 °C) unless otherwise noted. Thin-layer chromatography was performed on Merck 60 F₂₅₄ pre-coated silica gel plates, which were visualized by exposure to ultraviolet light (254 nm) or stained by submersion in aqueous ceric ammonium molybdate solution or ethanolic phosphomolybdic acid solution followed by brief heating on a hot plate (~200 °C, 10–15 s). Flash chromatography was performed as described by Still²¹ (silica gel: 60 Å, 230–400 mesh, Merck KGA). ¹H NMR spectra were

recorded at 500 or 600 MHz and ^{13}C NMR spectra at 125 MHz or 150 MHz with Bruker Avance spectrometers. Infrared spectra were recorded using an ASI ReactIRTM 1000 spectrometer. Mass spectra were measured with a Micromass LCT spectrometer. Melting points were determined using a Thomas Hoover Unimelt apparatus and are uncorrected.

2-Thioxo-1,3-diazaspiro[4.4]nonan-4-one: An ice-cooled solution of AcCl (3.0 mL, 42 mmol, 1.4 equiv) and MeOH (40 mL) was added to 1-aminocyclopentanecarboxylic acid (4.0 g, 31 mmol, 1 equiv), and the resulting solution was heated at reflux for 2.5 h. Half of the solvent was then removed in vacuo, and Et₂O (125 mL) was added to the remaining solution, precipitating methyl 1-aminocyclopentanecarboxylate hydrochloride, which was collected by filtration and dried in vacuo. CH₂Cl₂ (250 mL), Et₃N (33 mL, 240 mmol, 7.7 equiv), and benzoylthiocyanate (5.9 mL, 36 mmol, 1.2 equiv) were sequentially added to the dry solid, and the resulting solution was stirred at 23 °C for 4 h. The reaction solution was then washed with a 1:1 mixture of saturated aqueous NaHCO₃ solution–brine (200 mL). The organic layer was isolated, and the aqueous layer was extracted with CH₂Cl₂ (2×100 mL). The combined organic fractions were dried over MgSO₄ and concentrated in vacuo, affording methyl 1-(3-benzoylthioureido)cyclopentanecarboxylate (**5**) as a yellow-orange oil. MeOH (250 mL) and K₂CO₃ (1.5 g, 11 mmol, 0.35 equiv) were subsequently added to **5**, and the resulting solution was stirred at 23 °C for 15 h. The reaction solution was then concentrated to 40 mL final volume and partitioned between AcOEt (100 mL) and saturated aqueous NaHCO₃ solution (50 mL). The organic layer was isolated, and the aqueous layer was extracted with AcOEt (3×100 mL). The combined extracts were dried over Na₂SO₄ and concentrated in vacuo, affording a yellow solid. Recrystallization of the solid from hot CH₂Cl₂ afforded 2-thioxo-1,3-diazaspiro[4.4]nonan-4-one as a colorless solid (2.85 g, 54%, 3 steps):²² mp 190–193 °C; ^1H NMR (500 MHz, CDCl₃) δ 8.52 (br s, 1H, CONH), 7.77 (br s, 1H, CSNH), 2.20 (m, 2H, CCH₂), 1.94 (m, 4H, CCH₂CH₂), 1.83 (m, 2H, CCH₂CH₂); ^{13}C NMR (125 MHz, CDCl₃) δ 180.4, 104.8, 73.0, 37.7, 25.4; FTIR (film) 3301, 3098, 1734, 1518, 1406, 1319, 1269, 1235, 1196, 1148, 1069, 1005, 948, 761 cm⁻¹; HRMS (CI) m/z calcd for C₇H₁₀N₂OS (M)⁺: 170.0514, found: 170.0515.

1,3-Diaza-2-(methylthio)spiro[4.4]non-1-en-4-one (3): Aqueous NaOH (1.0 M, 16.5 mL, 16.5 mmol, 1 equiv) and MeI (1.6 mL, 26 mmol, 1.6 equiv) were sequentially added to a solution of 2-thioxo-1,3-diazaspiro[4.4]nonan-4-one (2.80 g, 16.5 mmol, 1 equiv) in MeOH (164 mL), and the resulting solution was stirred at 23 °C for 18 h. Brine (25 mL) was then added, and the resulting mixture was concentrated in vacuo to a volume of 35 mL. The residual solution was extracted with CHCl₃ (6×60 mL), and the combined extracts were dried over Na₂SO₄ and concentrated in vacuo. Chromatographic purification of the residue (60% AcOEt–hexanes→100% AcOEt) furnished diazaspirononenone (**3**) as a

colorless solid (2.49 g, 82%): mp 129–130 °C; ^1H NMR (600 MHz, CDCl_3) δ 9.20 (br s, 1H, CONH), 2.60 (s, 3H, SCH_3), 1.96 (m, 4H, CCH_2), 1.89 (m, 2H, CCH_2CH_2), 1.81 (m, 2H, CCH_2CH_2); ^{13}C NMR (CDCl_3 , 125 MHz) δ 187.6, 156.8, 78.9, 37.7, 26.2, 12.7; FTIR (film) 3032, 2950, 2872, 1709, 1499, 1443, 1414, 1340, 1277, 1159, 1073, 1022, 986 cm^{-1} ; HRMS (CI) m/z calcd for $\text{C}_8\text{H}_{12}\text{N}_2\text{OS}$ (M) $^+$: 184.0670, found: 184.0678.

9-Fluorenylmethyl 1,3-diaza-2-(methylthio)spiro[4.4]non-1-en-4-one-3-carboxylate: NaH (60% w/w in mineral oil, 163 mg, 4.08 mmol, 3.0 equiv) was added in one portion to a solution of diazaspirononenone (**3**) (250 mg, 1.36 mmol, 1 equiv) in THF (27 mL) at 0 °C. The resulting suspension was stirred at 0 °C for 10 min, then 9-fluorenylmethyl chloroformate (369 mg, 1.43 mmol, 1.05 equiv) was added, and the resulting solution was stirred at 0 °C for 5 min. Saturated aqueous NH_4Cl solution (10 mL) was carefully added to the reaction solution, and the resulting biphasic mixture was partitioned between AcOEt (90 mL) and half-saturated aqueous NH_4Cl solution (10 mL). The organic layer was separated, and the aqueous layer was extracted with AcOEt (2×30 mL). The combined organic extracts were dried over Na_2SO_4 and then concentrated in vacuo. Chromatographic purification of the residue (15%→25% AcOEt–hexanes) furnished 9-fluorenylmethyl 1,3-diaza-2-(methylthio)spiro[4.4]non-1-en-4-one-3-carboxylate as a colorless solid (507 mg, 92%): mp 135–136 °C; ^1H NMR (500 MHz, CDCl_3) δ 7.82 (d, 2H, $J = 7.4$ Hz, ArH), 7.79 (d, 2H, $J = 7.5$ Hz, ArH), 7.44 (t, 2H, $J = 7.4$ Hz, ArH), 7.37 (dt, 2H, $J = 1.1, 7.5$ Hz, ArH), 4.58 (d, 2H, $J = 7.5$ Hz, CO_2CH_2), 4.38 (t, 1H, $J = 7.5$ Hz, $\text{CO}_2\text{CH}_2\text{CH}$), 2.45 (s, 3H, SCH_3), 2.15–2.07 (m, 2H, CCH_2), 2.07–1.94 (m, 4H, CH_2CH_2), 1.94–1.85 (m, 2H, CCH_2CH_2); ^{13}C NMR (125 MHz, CDCl_3) δ 181.0, 156.8, 149.8, 143.3, 141.4, 128.1, 127.4, 125.6, 120.1, 78.4, 70.0, 46.5, 38.7, 26.1, 14.2; FTIR (film) 3066, 3043, 2960, 2873, 1777, 1736, 1574, 1452, 1383, 1298, 1236, 1172, 1118, 1023, 1003, 758, 741 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{23}\text{H}_{22}\text{O}_3\text{NaS}$ (M+Na) $^+$: 429.1249, found: 429.1248.

9-Fluorenylmethyl 1,3-diaza-2-(methylthio)spiro[4.4]non-1-en-4-ol-3-carboxylate (6):

9-Fluorenylmethyl 1,3-diaza-2-(methylthio)spiro[4.4]non-1-en-4-one-3-carboxylate (224 mg, 551 μmol , 1 equiv) was dissolved in MeOH (30 mL) with gentle heating, and the resulting solution was cooled to 0 °C. NaBH_4 (416 mg, 11.0 mmol, 20 equiv) was added in one portion, and the resulting solution was stirred at 0 °C for 10 min. AcOEt (10 mL), saturated aqueous NH_4Cl solution (8 mL), and water (2 mL) were sequentially added to the reaction solution, and the resulting biphasic mixture was allowed to warm to 23 °C. The mixture was then partitioned between AcOEt (150 mL) and half-saturated aqueous NH_4Cl solution (10 mL). The organic layer was separated, and the aqueous layer was extracted with AcOEt (2×50 mL). The organic extracts were combined and washed with brine (10 mL), then dried over

Na₂SO₄ and concentrated in vacuo. Chromatographic purification of the residue (25% AcOEt–hexanes) gave *N*-Fmoc diazaspirononol (**6**) as a colorless solid (194 mg, 86%): mp 129–131 °C; ¹H NMR (500 MHz, CDCl₃) δ 7.79 (dm, 2H, *J* = 7.5 Hz, ArH), 7.63 (d, 2H, *J* = 7.4 Hz, ArH), 7.43 (dd, 2H, *J* = 2.3, 7.4 Hz, ArH), 7.36 (ddt, 2H, *J* = 1.1, 2.3, 7.5 Hz, ArH), 5.01 (br s, 1H, NCHOH), 4.67 (d, 2H, *J* = 5.2 Hz, CO₂CH₂), 4.34 (t, 1H, *J* = 5.4 Hz, CO₂CH₂CH), 2.38 (s, 3H, SCH₃), 2.07 (m, 1H, CCH₂), 1.83 (m, 2H, CCH₂), 1.69 (m, 1H, CCH₂), 1.64 (m, 1H, CCH₂CH₂), 1.57 (m, 2H, CCH₂CH₂), 1.49 (m, 1H, CCH₂CH₂); ¹³C NMR (125 MHz, CDCl₃; minor rotamer denoted with *) δ 154.5, 151.5, 143.7*, 143.5, 141.5, 141.5*, 128.3*, 128.2, 127.6*, 127.6, 125.0*, 124.9, 120.3*, 120.3, 88.7, 80.3, 68.0, 47.1, 39.3, 31.4, 24.2, 23.7, 14.9; FTIR (film) 3459, 3067, 3040, 2955, 2874, 1724, 1570, 1451, 1396, 1351, 1301, 1245, 1146, 1088, 1024, 758, 741 cm⁻¹; HRMS (ESI) *m/z* calcd for C₂₃H₂₄N₂O₃NaS (M+Na)⁺: 431.1405, found: 431.1415.

1-(1-Formylcyclopentyl)-2-methylisothiourea (7): A solution of diazaspirononol (**6**) (59 mg, 150 μmol, 1 equiv) and 1,8-diazabicyclo[5.4.0]undec-7-ene (24 μL, 160 μmol, 1.1 equiv) in CH₂Cl₂ (7.25 mL) was stirred at 23 °C for 15 min, then directly chromatographically separated (30% AcOEt–hexanes + 2% Et₃N→70% AcOEt–hexanes + 2% Et₃N), furnishing 2-methylisothiourea (**7**) as a clear oil (23 mg, 85%): ¹H NMR (500 MHz, CDCl₃) δ 8.61 (s, 1H, CHO), 2.58 (s, 3H, SCH₃), 2.14–2.05 (m, 2H, CCH₂), 1.99–1.87 (m, 4H, CCH₂CH₂), 1.83–1.77 (m, 2H, CCH₂CH₂); ¹³C NMR (125 MHz, CDCl₃) δ 191.1, 173.1, 93.5, 32.9, 26.4, 14.5; FTIR (film) 3445, 3078, 2964, 2931, 2872, 1574, 1514, 1437, 1316, 1292, 1215, 1122, 1085, 954, 907, 695 cm⁻¹; HRMS (ESI) *m/z* calcd for C₈H₁₅N₂OS (M+H)⁺: 187.0905, found: 187.0903.

1,3-Diaza-2-methylthio-4-(phenylmethoxy)spiro[4.4]non-1-ene (8): 10-Camphorsulfonic acid (16 mg, 69 μmol, 0.8 equiv) was added in one portion to a suspension of 2-methylisothiourea (**7**) (16 mg, 86.0 μmol, 1 equiv), benzyl alcohol (13 μL, 130 μmol, 1.5 equiv), and 4Å molecular sieves (4 mg) in CH₂Cl₂ (2.1 mL) at 23 °C. After 100 min, the resulting solution was partitioned between CH₂Cl₂ (8 mL) and saturated aqueous NaHCO₃ solution (4 mL). The organic layer was separated, and the aqueous layer was extracted with CH₂Cl₂ (8 mL). The organic extracts were combined, dried over Na₂SO₄, and concentrated in vacuo. Chromatographic purification of the residue (40% AcOEt–hexanes + 2% Et₃N) furnished diazaspirononene (**8**) as a clear oil (16 mg, 55%): ¹H NMR (500 MHz, CDCl₃) δ 7.38 (m, 2H, ArH), 7.35 (d, 2H, *J* = 4.2 Hz, ArH), 7.31 (m, 1H, ArH), 4.98 (br s, 1H, NH), 4.71 (s, 2H, OCH₂), 4.56 (m, 1H, NCHO), 2.48 (br s, 3H, SCH₃), 2.34–1.98 (m, 2H, CCH₂), 1.98–1.73 (m, 2H, CCH₂), 1.73–1.43 (m, 4H, CCH₂CH₂); ¹³C NMR (125 MHz, CDCl₃) δ 141.2, 128.8, 127.8, 127.7, 127.2, 94.9, 70.1, 65.5, 38.9, 31.4, 24.7, 24.2, 13.8; FTIR (film) 3200, 3066, 3031, 2954, 2931, 2871, 1559, 1457, 1208, 1067, 1025, 735, 699 cm⁻¹; HRMS (ESI) *m/z* calcd for C₁₅H₂₁N₂OS (M+H)⁺: 277.1375, found: 277.1368.

1,3-Diaza-2-methylthio-3-[2-(trimethylsilyl)ethylsulfonyl]spiro[4.4]non-1-en-4-one (9): NaH (60% w/w in mineral oil; 65 mg, 1.6 mmol, 3.0 equiv) was added in one portion to a solution of diazaspirononenone (**3**) (100 mg, 540 μ mol, 1 equiv) in THF (10 mL) at 0 °C, and the resulting suspension was stirred for 5 min at 0 °C. 2-(Trimethylsilyl)ethylsulfonyl chloride (98 μ L, 570 μ mol, 1.0 equiv) was then added, and the resulting solution was stirred at 0 °C. After 5 min, saturated aqueous NH₄Cl solution (5 mL) was carefully added, and the resulting biphasic mixture was partitioned between AcOEt (40 mL) and water (5 mL). The organic layer was separated, and the aqueous layer was extracted with AcOEt (40 mL). The combined organic extracts were dried over Na₂SO₄ and concentrated in vacuo. Chromatographic purification of the residue (10%→25% AcOEt–hexanes) afforded *N*-SES-diazaspirononenone (**9**) as a colorless solid (124 mg, 66%): mp 72–75 °C; ¹H NMR (600 MHz, CDCl₃) δ 3.40 (m, 2H, SO₂CH₂), 2.45 (s, 3H, SCH₃), 1.98 (m, 4H, CCH₂), 1.92 (m, 2H, CCH₂CH₂), 1.84 (m, 2H, CCH₂CH₂), 1.00 (m, 2H, CH₂TMS), 0.06 (s, 9H, Si(CH₃)₃); ¹³C NMR (150 MHz, CDCl₃) δ 182.7, 155.2, 78.1, 50.8, 38.6, 26.0, 14.1, 10.0, –1.8; FTIR (film) 2925, 2896, 2873, 1760, 1569, 1370, 1252, 1196, 1154, 1113, 1073, 861, 843 cm^{–1}; HRMS (ESI) *m/z* calcd for C₁₃H₂₄N₂O₃NaS₂Si (M+Na)⁺: 371.0895, found: 371.0899.

2-[2-(Trimethylsilyl)ethylsulfonylamino]-1,3-diazaspiro[4.4]non-1-en-4-one (10): Ammonia was bubbled through a solution of *N*-SES-diazaspirononenone (**9**) (124 mg, 357 μ mol, 1 equiv) in MeOH (18 mL) at 0 °C in a sealable high-pressure vessel. After 3 min, the vessel was sealed, and the resulting solution was stirred at 23 °C for 1.5 h. The vessel was then cooled to 0 °C and opened, allowing excess ammonia to evaporate upon subsequent warming to 23 °C. Concentration of the reaction solution in vacuo furnished sulfonamide (**10**) as a colorless solid (104 mg, 92%). Recrystallization from a layered 1:1 AcOEt–Et₂O mixture (–20 °C) afforded colorless plates suitable for X-Ray diffraction: mp 170–173 °C; ¹H NMR (500 MHz, CDCl₃) δ 8.60 (br s, 1H, NH), 7.59 (br s, 1H, NH), 3.04 (m, 2H, SO₂CH₂), 2.19 (m, 2H, CCH₂), 1.93 (m, 4H, CCH₂CH₂), 1.84 (m, 2H, CCH₂CH₂), 1.05 (m, 2H, CH₂TMS), 0.07 (s, 9H, Si(CH₃)₃); ¹³C NMR (125 MHz, CDCl₃) δ 176.8, 155.2, 77.4, 51.1, 38.0, 25.5, 10.3, –1.7; FTIR (film) 3296, 2954, 1764, 1638, 1443, 1295, 1250, 1167, 1131, 855, 758, 702 cm^{–1}; HRMS (ESI) *m/z* calcd for C₁₂H₂₃N₃O₃NaSSi (M+Na)⁺: 340.1127, found: 340.1130.

2-[2-(Trimethylsilyl)ethylsulfonylamino]-1,3-diazaspiro[4.4]non-1-en-4-ol (11): Diisobutylaluminum hydride (1.0M in hexane, 100 μ L, 100 μ mol, 7.5 equiv) was added to a solution of sulfonamide (**10**) (4 mg, 13 μ mol, 1 equiv) in THF (1.0 mL) at –78 °C. After 10 min, the resulting solution was transferred to a 0 °C bath for 1 h. Saturated aqueous NH₄Cl solution (1 mL) and AcOEt (1 mL) were sequentially added to the reaction solution at 0 °C, and the resulting biphasic mixture was

allowed to warm to 23 °C. The mixture was then extracted with AcOEt (10 mL), and the organic layer was separated and sequentially washed with water (2×20 mL) and brine (2 mL). All aqueous layers were then combined and extracted with AcOEt (10 mL). All organic extracts were then combined, dried over Na₂SO₄, and concentrated in vacuo. Chromatographic purification of the residue (3% MeOH–CH₂Cl₂) provided *N*-SES diazaspirononenol (**11**) as a colorless solid (2 mg, 47%): mp 146–149 °C; ¹H NMR (500 MHz, CDCl₃) δ 7.45 (s, 1H, SO₂NH), 6.65 (s, 1H, CHNH), 4.98 (d, 1H, *J* = 4.8 Hz, CHOH), 4.15 (d, 1H, *J* = 5.6 Hz, OH), 2.94 (ddd, 2H, *J* = 3.4, 6.6, 14.6 Hz, SO₂CH₂), 2.28 (m, 1H, CCH₂), 1.87–1.64 (m, 7H, CCH₂CH₂), 1.03 (ddd, 2H, *J* = 4.3, 7.2, 15.0 Hz, CH₂TMS), 0.05 (s, 9H, Si(CH₃)₃); ¹³C NMR (125 MHz, CDCl₃) δ 158.6, 84.4, 72.0, 50.9, 38.6, 30.7, 23.5, 23.4, 10.5, –1.7; FTIR (film) 3338, 2955, 2875, 1605, 1497, 1247, 1131, 1077, 1023, 840, 755, 700 cm^{–1}; HRMS (ESI) *m/z* calcd for C₁₂H₂₅N₃O₃NaSSi (M+Na)⁺: 342.1284, found: 342.1283.

1,3-Diaza-2-methylthio-3-(4-methoxybenzenesulfonyl)spiro[4.4]non-1-en-4-one (12): NaH (27 mg, 680 μmol, 2.5 equiv) was added in one portion to an ice-cooled solution of diazaspirononenone (**3**) (50.0 mg, 271 μmol, 1 equiv) in THF (10.0 mL). After 10 min, 4-methoxybenzenesulfonyl chloride (140 mg, 680 μmol, 2.5 equiv) was added, and the resulting solution was stirred at 0 °C for 10 min. Saturated aqueous NH₄Cl solution (1 mL) was then slowly added at 0 °C to quench excess NaH, and the resulting mixture was partitioned between AcOEt (10 mL) and half-saturated aqueous NH₄Cl solution (3 mL). The organic layer was separated, and the aqueous layer was extracted with AcOEt (2×10 mL). All organic extracts were then combined, dried over Na₂SO₄, and concentrated in vacuo. Chromatographic purification of the residue (20%→30% AcOEt–hexanes) provided diazaspirononenone (**12**) as a colorless solid (86 mg, 89%): mp 90–92 °C; ¹H NMR (500 MHz, CDCl₃) δ 8.03 (d, 2H, *J* = 8.9 Hz, SO₂CCH), 7.01 (d, 2H, *J* = 8.9 Hz, CHCOCH₃), 3.88 (s, 3H, OCH₃), 2.44 (s, 3H, SCH₃), 1.90–1.81 (m, 6H, CCH₂CH₂), 1.74–1.71 (m, 2H, CCH₂CH₂); ¹³C NMR (125 MHz, CDCl₃) δ 181.5, 164.7, 155.1, 130.8, 129.1, 114.6, 77.8, 56.0, 38.3, 25.9, 14.1; FTIR (film) 3105, 2954, 2873, 1769, 1595, 1567, 1498, 1378, 1266, 1199, 1164, 1091, 1022, 972, 835, 805, 674 cm^{–1}; HRMS (ESI) *m/z* calcd for C₁₅H₁₈N₂O₄NaS₂ (M+Na)⁺: 377.0606, found: 377.0611.

1-[1-(Hydroxymethyl)cyclopentyl]-3-(4-methoxybenzenesulfonyl)-2-methylisothiurea (13): NaBH₄ (2.0 mg, 53 μmol, 1.3 equiv) was added in one portion to a solution of diazaspirononenone (**12**) (15 mg, 42 μmol, 1.0 equiv) in MeOH (0.5 mL) at 0 °C. After 1 h, AcOEt (2 mL) was added to the reaction solution, followed by half-saturated aqueous NH₄Cl solution (2 mL). The resulting biphasic mixture was allowed to warm to 23 °C and was then partitioned between AcOEt (15 mL) and water (2 mL). The organic layer was separated, and the aqueous layer was extracted with AcOEt (2×10 mL).

The organic extracts were combined, dried over Na_2SO_4 , and concentrated in vacuo. Chromatographic purification of the residue (70% AcOEt–hexanes) provided *N*-SES pseudothiourea (**13**) as a clear oil (15 mg, 100%): ^1H NMR (600 MHz, CDCl_3) δ 8.37 (br s, 1H, **NH**), 7.86 (dt, 2H, $J = 3.0, 8.4$ Hz, SO_2CCH), 6.95 (dt, 2H, $J = 3.0, 9.0$ Hz, SO_2CCHCH), 3.86 (s, 3H, OCH_3), 3.72 (s, 2H, CH_2OH), 2.39 (s, 3H, SCH_3), 1.96 (m, 2H, CCH_2), 1.85 (m, 2H, CCH_2), 1.70 (m, 2H, CCH_2CH_2), 1.63 (m, 2H, CCH_2CH_2); ^{13}C NMR (125 MHz, CDCl_3) δ 162.6(2), 134.5, 128.6, 114.1, 68.5, 65.7, 55.8, 36.1, 24.5, 15.1; FTIR (film) 3396, 2958, 2873, 1567, 1499, 1256, 1140, 1088, 834, 805, 704 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{15}\text{H}_{22}\text{N}_2\text{O}_4\text{NaS}_2$ ($\text{M}+\text{Na}$) $^+$: 381.0919, found: 381.0919.

Benzyl 1,3-diaza-2-(methylthio)spiro[4.4]non-1-en-4-one-3-carboxylate: NaH (60% w/w in mineral oil, 270 mg, 6.8 mmol, 2.5 equiv) was added in one portion to a solution of 1,3-diaza-2-(methylthio)spiro[4.4]non-1-en-4-one (**3**) (500 mg, 2.70 mmol, 1.0 equiv) in THF (35 mL) at 0 °C. After 10 min, benzyl chloroformate (410 μL , 2.9 mmol, 1.1 equiv) was added, and the resulting solution was stirred at 0 °C for 5 min. Saturated aqueous NH_4Cl solution (8 mL) was then added, and the resulting biphasic mixture was partitioned between AcOEt (120 mL) and half-saturated aqueous NH_4Cl solution (20 mL). The organic layer was isolated, and the aqueous layer was extracted with AcOEt (2 $\times$ 100 mL). All organic extracts were then combined, dried over Na_2SO_4 , and concentrated in vacuo. Chromatographic purification of the residue (20% $\rightarrow$ 30% AcOEt–hexanes) provided benzyl 1,3-diaza-2-(methylthio)spiro[4.4]non-1-en-4-one-3-carboxylate as a colorless solid (819 mg, 95%). Recrystallization from Et_2O (23 °C) afforded colorless spars suitable for X-Ray diffraction: mp 111–112 °C; ^1H NMR (500 MHz, CDCl_3) δ 7.49 (d, 2H, $J = 6.9$ Hz, **ArH**), 7.41–7.34 (m, 3H, **ArH**), 5.38 (s, 2H, OCH_2Ph), 2.43 (s, 3H, SCH_3), 2.05–1.93 (m, 4H, CCH_2), 2.93–1.86 (m, 2H, CCH_2CH_2), 1.84–1.76 (m, 2H, CCH_2CH_2); ^{13}C NMR (125 MHz, CDCl_3) δ 181.1, 156.7, 149.6, 134.5, 128.9(2), 128.5, 78.4, 69.3, 38.7, 26.1, 14.3; FTIR (film) 3064, 3035, 2958, 2873, 1775, 1737, 1574, 1457, 1382, 1297, 1229, 1171, 1119, 1000, 766, 735, 697 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{16}\text{H}_{18}\text{N}_2\text{O}_3\text{NaS}$ ($\text{M}+\text{Na}$) $^+$: 341.0936, found: 341.0923.

Benzyl 1,3-diaza-2-(methylthio)spiro[4.4]non-1-en-4-ol-3-carboxylate (14**):** NaBH_4 (230 mg, 6.2 mmol, 10 equiv) was added in one portion to a solution of benzyl 1,3-diaza-2-(methylthio)spiro[4.4]non-1-en-4-one-3-carboxylate (197 mg, 619 μmol , 1.0 equiv) in MeOH (8 mL) at 0 °C. The resulting suspension was stirred at 0 °C for 5 min and was then diluted with AcOEt (10 mL). Saturated aqueous NH_4Cl solution (8 mL) and water (2 mL) were sequentially added, and the resulting biphasic mixture was allowed to warm to 23 °C. The mixture was then partitioned between AcOEt (30 mL) and water (2 mL). The organic layer was isolated, and the aqueous layer was extracted

with AcOEt (2×30 mL). All organic extracts were then combined, dried over Na₂SO₄, and concentrated in vacuo. Chromatographic purification of the residue (30%→40% AcOEt–hexanes) furnished **14** as a colorless solid (176 mg, 88%): mp 138–139 °C; ¹H NMR (500 MHz, CDCl₃) δ 7.42–7.34 (m, 5H, ArH), 5.38 (s, 1H, NCHOH), 5.26 (dd, 2H, *J* = 12.2, 16.7 Hz, CO₂CH₂), 2.41 (s, 3H, SCH₃), 2.15 (m, 1H, CCH₂), 1.86 (m, 2H, CCH₂), 1.77 (m, 1H, CCH₂), 1.60 (m, 4H, CCH₂CH₂); ¹³C NMR (125 MHz, CDCl₃) δ 154.4, 151.6, 135.2, 128.9, 128.8, 128.6, 88.7, 80.4, 68.4, 39.2, 31.4, 24.2, 23.7, 15.0; FTIR (film) 3438, 3066, 3035, 2960, 2871, 1719, 1573, 1391, 1351, 1301, 1144, 1082, 1023, 766, 699 cm⁻¹; HRMS (ESI) *m/z* calcd for C₁₆H₂₁N₂O₃S (M+H)⁺: 321.1273, found: 321.1270.

Benzyl 2-amino-1,3-diazaspiro[4.4]non-1-en-4-ol-3-carboxylate (15): Ammonia (7.0 mL, 280 mmol, 1000 equiv) was condensed into a solution of **14** (90 mg, 280 μmol, 1.0 equiv) in THF (3 mL) in a glass-lined stainless-steel high-pressure vessel at –78 °C. The vessel was then sealed and heated at 80 °C for 1 d. After cooling to –78 °C, the vessel was opened, excess ammonia was allowed to evaporate with warming to 23 °C, and the resulting solution was concentrated in vacuo. Chromatographic purification of the residue (20→40→60% THF–CH₂Cl₂)²³ yielded **15** as a colorless solid (55 mg, 68%): mp 154–156 °C; ¹H NMR (600 MHz, CDCl₃) δ 7.90 (br s, 1H, NH₂), 7.67 (br s, 1H, NH₂), 7.39 (d, 2H, *J* = 7.1 Hz, ArH), 7.35 (t, 2H, *J* = 7.1 Hz, ArH), 7.31 (t, 1H, *J* = 7.1 Hz, ArH), 5.09 (dd, 2H, *J* = 12.6, 15.9 Hz, CO₂CH₂), 4.84 (s, 1H, NCHOH), 2.16 (m, 1H, CCH₂), 1.79 (m, 1H, CCH₂), 1.72–1.64 (m, 2H, CCH₂), 1.64–1.53 (m, 4H, CCH₂CH₂); ¹³C NMR (125 MHz, CD₃OD) δ 164.9, 163.8, 138.9, 129.5, 128.9(2), 85.8, 72.2, 67.6, 39.4, 31.3, 24.4, 24.2; FTIR (film) 3384, 2954, 2875, 1648, 1615, 1497, 1455, 1383, 1328, 1277, 1237, 1090, 1077, 1028, 801, 743, 699 cm⁻¹; HRMS (ESI) *m/z* calcd for C₁₅H₂₀N₃O₃ (M+H)⁺: 290.1505, found: 290.1498.

2-Amino-1,3-diazaspiro[4.4]non-1-en-4-ol, acetic acid salt (2): 10% Palladium on activated carbon (50% w/w water; 54.0 mg, 25.4 μmol, 0.15 equiv) was added to an argon-sparged solution of **15** (49 mg, 170 μmol, 1.0 equiv) and AcOH (29 μL, 510 μmol, 3.0 equiv) in THF (5.6 mL) at 23 °C. The flask containing the resulting suspension was alternately evacuated (1 torr) and refilled with hydrogen (1 atm) (3×), and the resulting suspension was then stirred under hydrogen atmosphere (1 atm) at 23 °C for 1 h. Filtration of the resulting suspension through a Celite pad (subsequently washed with 50 mL of THF), followed by concentration of the filtrate, afforded **2** as a waxy, colorless solid (33 mg, 73%): ¹H NMR (500 MHz, CDCl₃) δ 8.22 (br s, 1H, NH), 7.92 (br s, 2H, NH₂), 6.51 (br s, 2H, CHOH, CO₂H), 4.95 (s, 1H, NCHOH), 2.21 (m, 1H, CCH₂), 2.03 (s, 3H, COCH₃), 1.81–1.77 (m, 3H, CCH₂), 1.77–1.64 (m, 4H, CCH₂CH₂); ¹³C NMR (125 MHz, CDCl₃) δ 179.0, 158.2, 86.1, 73.3, 38.6, 30.6, 23.5(2), 23.5; FTIR (film)

3174, 2960, 2919, 2850, 1690, 1563, 1409, 1262, 1086, 1021, 799 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_7\text{H}_{14}\text{N}_3\text{O}$ ($\text{M}+\text{H}$)⁺: 156.1137, found: 156.1136.

ACKNOWLEDGMENTS

Support from the National Heart, Lung, and Blood Institute (HL-25854) and NIH NRSA postdoctoral fellowship support to B.A.L. (GM-71132) are gratefully acknowledged. We also thank Bruce N. Rogers, Fang-Tsao Hong, and Patrick W. Papa for preliminary experiments in this area. Joseph Ziller is acknowledged for assistance with X-Ray crystallography.

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6. An alternative preparation of 2-thioxo-1,3-diazaspiro[4.4]nonan-4-one has previously been reported: H. C. Carrington, C. H. Vasey, and W. S. Waring, *J. Chem. Soc.*, 1953, 3105. This compound is also available commercially from Chemstep.
7. The position of the *N*-acyloxy protective group in **6** (and the *N*-sulfonyl protective groups in **9** and **12**) is assigned by analogy with benzyl 1,3-diaza-2-(methylthio)spiro[4.4]non-1-en-4-one-3-carboxylate, whose structure was established by X-Ray crystallography.
8. Exposure of **8** to ethanolic ammonium chloride (75 °C, 19 h) exclusively led to the generation of the corresponding *O*-ethyl hemiaminal.
9. Prepared by the oxidation of pseudothiourea (**8**) with dimethyldioxirane (DMDO). Attempts to convert **8** to the corresponding sulfone using 3-chloroperoxybenzoic acid afforded only recovered starting material.
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12. Aminolysis of **9** initially generates the ring-opened primary amide, which subsequently cyclizes to *N*-SES glycohydrazide (**10**). The structure of **10** has been confirmed by X-Ray crystallography.
13. The deoxoguanidine analog of **10** is the major by-product of this reaction.
14. The resistance of glycohydrazides bearing acidic hydrogens to metal hydride-mediated reduction has previously been reported: J. F. Stearns and H. Rapoport, *J. Org. Chem.*, 1977, **42**, 3608.
15. Direct aminolysis of *S*-methylated thiohydantoin (**3**) (NH₃, EtOH, 80 °C, 24 h) afforded a related, unprotected glycohydrazide; however, subsequent reduction of this product to the corresponding guanidine hemiaminal (PtO₂/H₂) proved unsuccessful (cf., M. M. Wegner and H. Rapoport, *J. Org. Chem.*, 1978, **43**, 3840). Cbz-protection of this related glycohydrazide facilitated reduction to the corresponding guanidine hemiaminal (NaBH₄); however, low yields for this process and complicated ¹H NMR spectra of the protected intermediates (Cbz rotamers) rendered this route to guanidine hemiaminal (**2**) unattractive.
16. The use of *N*-Fmoc pseudothiourea (**6**) in such a strategy was precluded by the base-lability of the *N*-Fmoc group.
17. A large excess of sodium borohydride was employed in the reduction step to favor reduction over competitive methoxide-mediated Cbz cleavage and imide solvolysis processes.
18. As before, no over-reduction product was observed in this two-step process. The only by-product of this process was *S*-methylated thiohydantoin (**3**), which arose from cleavage of the Cbz group from *N*-Cbz (**3**) prior to reduction.
19. The C4-amino analog of **15** was the sole by-product detected in this reaction.
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22. Alternatively, chromatographic purification of the crude product (35→40→50% AcOEt–hexanes) afforded 2-thioxo-1,3-diazaspiro[4.4]nonan-4-one in 85% yield (3 steps).
23. Substitution of MeOH for THF as an eluent resulted in partial conversion of **15** to the corresponding *O*-methyl hemiaminal during chromatography.