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SYNTHESIS OF A CYCLIC GUANIDINE HEMIAMINAL PERTINENT TO THE AXINELLAMINES‡

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Abstract – Potential methods for the generation of the cyclic guanidine hemiaminal functionality of axinellamine A (**1**) from a hydantoin precursor are examined. An activation-reduction sequence was developed for the reduction of cyclic acyl guanidines.

‡Dedicated to Prof. Dr. Ekkehard Winterfeldt on the occasion of his 75th birthday and his excellent contributions to heterocyclic chemistry.

INTRODUCTION

The complex marine natural product, axinellamine A (**1**), was isolated by Quinn and coworkers in 1999 from *axinella sp.*[1] following the isolation of the biosynthetically related alkaloid, palau'amine.[2] Despite several synthetic investigations toward axinellamine and palua'amine in the intervening years,[3] total syntheses of these targets have not been reported. During our efforts toward the total synthesis of the axinellamines (*e.g.* axinellamine A, **1**),[4] we required strategies for construction of the spiro guanidine hemiaminal (2-aminoimidazolin-5-ol) functionality found in the axinellamines (Figure 1).

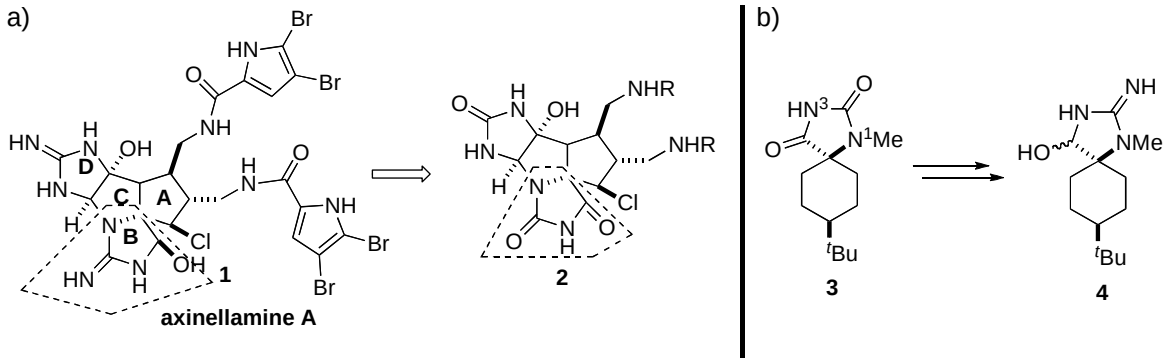
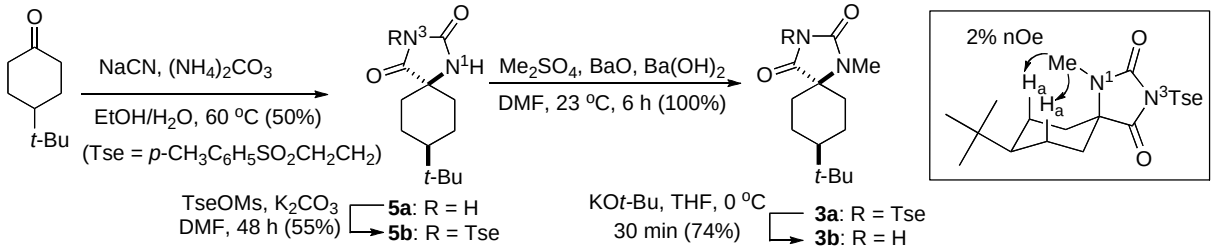


Figure 1. a) Structures of axinellamine A (**1**) and possible precursor **2** with the cyclic guanidine hemiaminal sub-structure and hydantoin precursor highlighted. b) Model system for conversion of N^1-alkyl hydantoins (*e.g.* **3**) to cyclic guanidine hemiaminals (*e.g.* **4**).

In one retrosynthetic strategy toward the axinellamines, hydantoin **2** would serve as an advanced intermediate. Thus, we sought to develop various strategies for transformation of N^1-alkylated bicyclic hydantoins *e.g.* hydantoin **3** to cyclic guanidine hemiaminals *e.g.* **4**. Recently, Overman reported independent studies toward conversion of N^1-unsubstituted 2-thiohydantoins to guanidine hemiaminals.[5] Herein, we report our parallel studies for the conversion of N^1-alkylated hydantoins that requires an activation-reduction sequence to prepare the requisite cyclic guanidine hemiaminal found in the axinellamines.

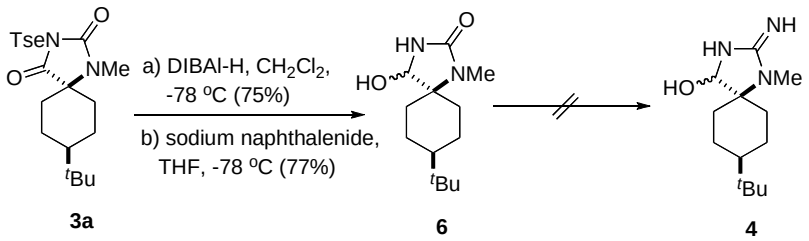
RESULTS AND DISCUSSION

The model compound, N^1-methyl hydantoin **3b**, was prepared from commercially available 4-*t*-butyl cyclohexanone (Scheme 1). The synthesis of this model system began with a Bucherer-Bergs reaction,[6] followed by blocking of the N^3 position with a tosylethyl group to furnish hydantoin **5b**. This enabled efficient methylation at the N^1 position to provide dialkylated hydantoin **3a**. The relative stereochemistry of hydantoin **3a** was determined by nOe enhancements observed for H_a (assigned by COSY) when the N^1-methyl group was irradiated (Scheme 1, inset). The Tse protecting group could be easily removed with base[7] to provide the N^1-methyl hydantoin **3b**.



Scheme 1. Preparation of a model N^1-alkyl hydantoin **3b**

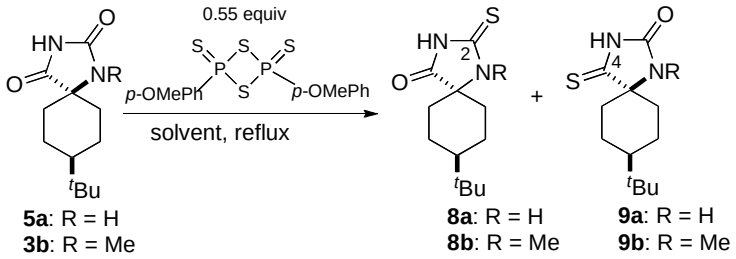
The initial approach studied for conversion of a hydantoin to a cyclic guanidine hemiaminal such as **4** involved reduction to a hemiaminal prior to guanidinylation. The bis-alkylated hydantoin **3a** could be smoothly reduced to the corresponding hemiaminal with DIBAl-H (Scheme 2). However, after removal of the Tse group, the mono-alkylated urea hemiaminal **6** was found to be unstable and attempted guanidinylation under a variety of conditions including Lawesson's reagent,[8] Belleau's reagent,[9] $POCl_3$[10] and direct amination with BOP[11] led to extensive decomposition.



Scheme 2. Attempted reduction of bis-alkylated hydantoin **3a**

These results led us to explore an alternative strategy involving initial introduction of the guanidine followed by reduction to the hemiaminal. We found that mono-thiolation of N^1, N^3-unsubstituted hydantoin **5a** occurred readily to provide 2-thiohydantoin **8a** employing Lawesson's reagent[12] (Table 1, entry 1). However, applying these conditions to the N^1-methylated hydantoin **3b**, gave only the 4-thiohydantoin **9b** under the same conditions likely due to steric issues (Table 1, entry 2). Ultimately, it was found that use of a non-polar solvent greatly increased the product distribution in favor of the desired 2-thiohydantoin **8b** with benzene giving slightly better results over toluene (*cf*. Table 1, entry 3 versus 5). Under optimized conditions, the 2-thiohydantoin **8b** could be obtained in 65% yield after refluxing in benzene (Table 1, entry 5) while reactions at 23 ^{o}C gave high regioselectivity but only low conversion (Table 1, entry 6). The two regio-isomers are readily separated and differentiated by ^{13}C NMR analysis based on chemical shift differences for the C^2 and C^4 oxo- versus thio-carbonyl carbons.

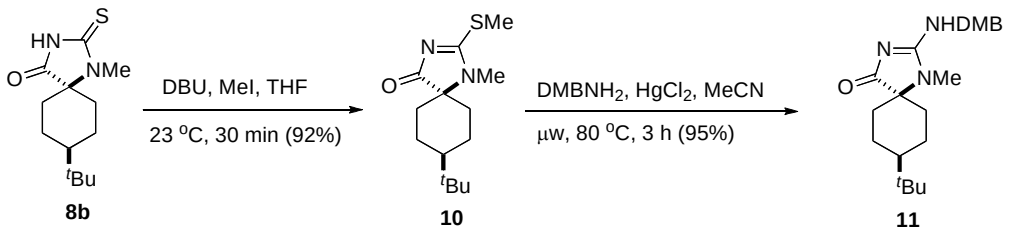
Table 1. Thiolation of hydantoins **5a** and **3b**.



entry	substrate	solvent	% yield (**8a** or **8b**)[a]	%yield (**9a** or **b**)[a]
1	**5a**	dioxane	88	0
2	**3b**	dioxane	trace	60
3	**3b**	toluene	56	30
4	**3b**[b]	toluene	20	0
5	**3b**	benzene	65	25
6	**3b**	benzene[c]	~5	0

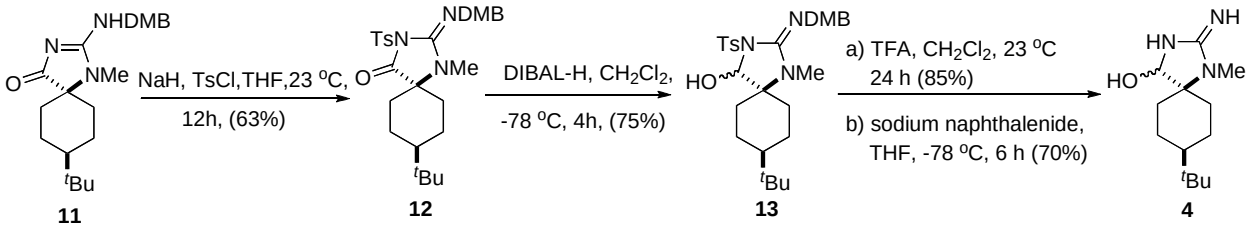
[a] Yields refer to isolated, purified products. [b] 1.0 equiv of Lawesson's reagent was used. [c] Reaction was conducted at 23 ^{o}C.

Subsequent methylation of 2-thiohydantoin **8b** proceeded smoothly to furnish isothiourea **10** (Scheme 3). Following aminolysis using microwave irradiation with 3,4-dimethoxy benzylamine, protected oxo-guanidine **11** was obtained. While similar aminations are well known in the literature,[13] this conversion required harsh conditions likely due to the steric effects of the N^1-methyl group.



Scheme 3. Guanidinylation of 2-thiohydantoin **8b**

Reduction of the oxo-guanidine **11** would provide the target cyclic guanidine hemiaminal. Only a few examples of similar reductions can be found in the literature typically resulting in overreduction to the corresponding methylene derivative.[14] Overman's protocol[5] is not readily applied here since N^1 is substituted. Initial studies, with oxo-guandine **11** revealed that this substrate was inert to many reducing agents. This is likely due to two factors: (1) the electron rich nature of the guanidine which is in conjugation with the carbonyl and (2) the acidic proton of the exocyclic nitrogen which upon deprotonation renders the carbonyl even less reactive. We recognized that introduction of an electron-withdrawing substituent on nitrogen might facilitate the reduction by removing the acidic proton and also activating the amide carbonyl for reduction. Indeed, tosylation of N^3 gave the protected oxo-guanidine **12**. Reduction of this substrate with DIBAL-H proceeded smoothly to give the desired hemiaminal even at low temperature as a racemic mixture. Interestingly, both the Cbz (carbobenzyloxy) and Boc (*t*-butoxycarbonyl) protected oxo-guanidines could also be prepared in high yields, however these were found to be inert to reduction under similar conditions utilized for the tosyl protected system. Finally, removal of the protecting groups in a two-step sequence using trifluoroacetic acid (TFA) followed by sodium naphthalide yielded the target guanidine hemiaminal **4**.

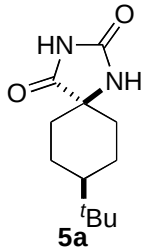


Scheme 4. Activation and reduction of cyclic oxo-guanidine **11**

In conclusion, we have developed a strategy for the conversion of N^1-alkyl hydantoins to the corresponding guanidine hemiaminal that is applicable to this key subunit found in axinellamine A. For efficient reduction, the oxo-guanidine moiety required activation by use of a *p*-toluenesulfonyl group at N^3 of the cyclic guanidine. This strategy for the synthesis of N^1-alkylated guanidine hemiaminals complements procedures recently reported by Overman for N^1-unsubstituted guanidine hemiaminals.[5]

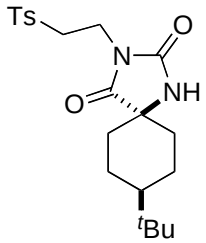
EXPERIMENTAL

8-^{t}Bu-1,3-diazaspiro[4.5]decane-2,4-dione (5a): NaCN (5.1 g, 104 mmol), 4-^{t}Bu-cyclohexanone (10.0 g, 64 mmol) and ammonium carbonate (22g, 235 mmol) was dissolved in a mixture solvent of EtOH and water (250 mL, 1:1). The reaction mixture was heated to 60 °C for 12 h. After cooling to 23 °C, the EtOH was removed under reduced pressure and the precipitated was filtered to deliver crude product. This white solid was recrystallized from EtOH/H_2O to afford the desired product as colorless crystals (7.9 g, 55%): mp 236 - 238 °C; IR (thin film)



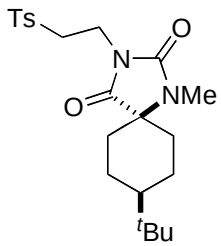
3262, 3179, 2957, 1776, 1726 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 1.88-1.70 (m, 6H), 1.31 (dq, *J* = 13.0, 4.0 Hz, 2H), 1.13 (apparent tt, *J* = 12.0, 3.0 Hz, 1H), 0.93 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 179.7, 157.4, 63.1, 47.4, 34.6, 33.1, 28.3, 22.8; ESI HRMS calcd for $C_{12}H_{21}N_2O_2$ [M+H] 225.1603, found 225.1606.

8-^{t}Bu-3-(2-tosylethyl)-1,3-diazaspiro[4.5]decane-2,4-dione (**5b**): To a solution of 8-^{t}Bu-1,3-diazaspiro[4.5]decane-2,4-dione (**5a**) (2.0 g, 8.9 mmol) in DMF (100 mL) was added TseOMs (3.0 g, 11 mmol) and K_2CO_3 (1.5 g, 11 mmol, anhydrous). The reaction mixture was stirred at 23 °C for 3 days. Water was added and the mixture was extracted with EtOAc 3 times. The combined organic phase was washed with water (3 times) and brine, dried over anhydrous Na_2SO_4 and concentrated to afford the crude product as a white solid. Recrystallization from EtOAc/EtOH gave the protected hydantoin **5b** as a colorless crystalline solid (2.0 g, 55%): mp 302 -305 °C; R_f 0.35 (2:1, hexanes:ethyl acetate); IR (thin film) 3221, 2951, 1764, 1714 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 3.80 (t, *J* = 6.5 Hz, 2H), 3.46 (t, *J* = 8.5 Hz, 2H), 2.44 (s, 3H), 1.86-1.76 (m, 4H), 1.72-1.64 (m, 2H), 1.22-1.08 (m, 3H), 0.87 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.9, 156.7, 145.3, 135.5, 130.2, 128.6, 62.4, 52.4, 46.5, 33.6, 32.8, 32.6, 27.5, 22.7, 21.8; ESI HRMS calcd for $C_{21}H_{31}N_2O_4S$ [M + H] 407.2005, found 407.2015.



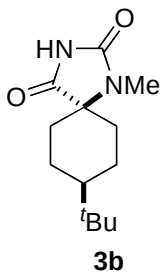
5b

8-^{t}Bu-1-methyl-3-(2-tosylethyl)-1,3-diazaspiro[4.5]decane-2,4-dione (3a): Barium oxide (6.0 g, 39 mmol) and barium hydroxide octahydrate (3.5 g, 11 mmol) were added to a stirred solution of 8-^{t}Bu-3-(2-tosylethyl)-1,3-diazaspiro[4.5]decane -2,4-dione (**5b**) (2.5 g, 6 mmol) in DMF (80 mL) at 23 °C. Dimethyl sulfate (14.0 mL, 150 mmol) was added dropwise and the mixture was stirred at 23 °C for 6 h and set aside overnight. The mixture was them partitioned between EtOAc and water and the EtOAc layer was separated repeatedly washed with water and then dried over anhydrous Na_2SO_4 and concentrate to afford the desired product as a white solid (2.5g, 96%). This product was of sufficient purity to be used directly in the next reaction without further purification: R_f 0.55 (5:95, ethyl acetate:CH_2Cl_2); IR (thin film) 2960, 1767, 1711 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.0 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 3.81 (t, *J* = 6.5 Hz, 2H), 3.46 (t, *J* = 6.5 Hz, 2H), 3.18 (s, 3H), 2.45 (s, 3H), 1.98 (dt, *J* = 9.0, 4.5 Hz, 2H), 1.88-1.82 (m, 4H), 1.39 (dq, *J* = 13.0, 2.5 Hz, 2H), 1.20 (apparent tt, *J* = 13.0, 3.5Hz, 1H), 0.89 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.6, 155.2, 145.2, 135.5, 130.1, 128.7, 63.0, 52.4, 46.0, 33.4, 33.3, 32.6, 29.6, 27.5, 23.2, 21.8; ESI HRMS calcd for $C_{22}H_{33}N_2O_4S$ [M+H] 421.2141, found 421.2131



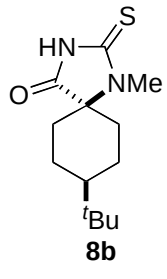
3a

8-^{t}Bu-1-methyl-1,3-diazaspiro[4.5]decane-2,4-dione (3b): To an ice-cooled solution of 8-^{t}Bu-1-methyl-3-(2-tosylethyl)-1,3-diazaspiro[4.5]decane-2,4-dione (**3a**) (420 mg, 1.0 mmol) in THF (10 mL) was added potassium tert-butoxide (1.0 M in THF, 5 mL). The resulting mixture was stirred at 0 ^{o}C for 30 min and TLC shows no starting material left. Water was added and the aqueous phase was extracted with EtOAc three times. The combined organic phase was washed with brine, dried with anhydrous Na_2SO_4 and concentrated in vacuo, affording a brown solid. Purification of the residue by flash column chromatography (20% EtOAc in CH_2Cl_2) furnished the desired product as a white foam (175 mg, 74%): R_f 0.33 (20:80, EtOAc:CH_2Cl_2) IR (thin film) 3162, 2949, 1767, 1702 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.98 (br, 1H), 3.15 (s, 3H), 2.00 (dt, *J* = 14.5, 5.0 Hz, 2H), 1.91 (t, *J* = 2.0 Hz, 2H), 1.89-1.82 (m, 2H), 1.40 (dq, *J* = 13.0, 4.0 Hz, 2H), 1.18, (apparent tt, *J* = 12.0, 3.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.9, 156.1, 64.3, 45.9, 33.5, 32.6, 29.3, 27.4, 23.1. ESI HRMS calcd for $C_{13}H_{23}N_2O_2$ [M+H] 239.1760, found 239.1758.



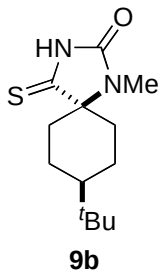
3b

8-^{t}Bu-1-methyl-2-thioxo-1,3-diazaspiro[4.5]decan-4-one (8b): Lawesson's reagent (111 mg, 0.28 mmol) was added to the solution of 8-^{t}Bu-1-methyl-1,3-diazaspiro[4.5]decane-2,4-dione (**3b**) (120 mg, 0.5 mmol) in benzene (5 mL). The resulting mixture was heated to refluxing for 6 h and cooled to 23 ^{o}C. The solvent was removed in vacuo and the residue was purified by flash column chromatography (2% EtOAc in CH_2Cl_2), affording the thiohydantoin **8b** as a white solid (81 mg, 64%): R_f 0.35 (2:98, ethyl acetate:CH_2Cl_2), IR (thin film) 3150, 2949, 1752, 1726 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.39 (br, 1H), 3.48 (s, 3H), 2.02-1.82 (m, 6H), 1.42 (dq, *J* = 13.0, 5.0 Hz, 1H), 1.20 (apparent tt, *J* = 12.0, 3.5 Hz, 1H), 0.88 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.1, 177.6, 67.2, 45.6, 33.8, 32.9, 32.6, 27.4, 22.5. ESI HRMS calcd for $C_{13}H_{23}N_2OS$ [M+H] 255.1531, found 255.1535.



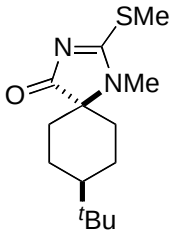
8b

8-^{t}Bu-1-methyl-4-thioxo-1,3-diazaspiro[4.5]decan-2-one (9b): This compound was obtained as a by-product with thiohydantoin **8b**: R_f 0.18 (2:98, EtOAc:CH_2Cl_2); IR (thin film) 3082, 2954, 1720 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.50 (br, 1H), 3.24 (s, 3H), 2.25 (dt, *J* = 14.5, 5.0 Hz, 2H), 1.93-1.84 (m, 4H), 1.46 (dq, *J* = 13.5, 3.5 Hz, 2H), 1.26 (apparent tt, *J* = 12.0, 4.0 Hz, 1H), 0.90 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.4, 156.0, 73.5, 45.9, 38.0, 32.7, 30.6, 27.5, 23.5; ESI HRMS calcd for $C_{13}H_{23}N_2OS$ [M+H] 255.1531, found 255.1532.



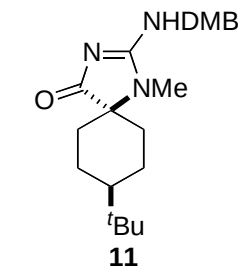
9b

8-^{t}Bu-1-methyl-2-(methylthio)-1,3-diazaspiro[4.5]dec-2-en-4-one (10): To a solution of 8-^{t}Bu-1-methyl-2-thioxo-1,3-diazaspiro[4.5]decan-4-one (**8b**) (32 mg, 0.12 mmol) in THF (5 mL) was added DBU (35 µL, 0.24 mmol) and MeI (14 µL, 0.24 mmol). The resulting mixture was stirred at 23 ^{o}C for 30 min and concentrated in vacuo. The residue was purified by flash column chromatography (50% EtOAc in Hexane) to afford the desired product as a white foam (31 mg, 92%): R_f 0.25 (30:70, ethyl acetate:hexanes); IR (thin film) 2966, 2943, 1708 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.30 (s, 3H), 1.97 (dt, *J* = 15.0, 5.0 Hz, 2H), 1.88-1.78 (m, 4H), 1.36 (dq, *J* = 12.0, 4.0 Hz, 2H), 1.22 (apparent tt, *J* = 12.0, 4.0 Hz, 1H), 0.88 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.1, 183.5, 69.0, 46.1, 33.7, 33.5, 32.6, 27.4, 23.1, 15.1; ESI HRMS calcd for $C_{14}H_{25}N_2OS$ [M+H] 269.1688, found 269.1690



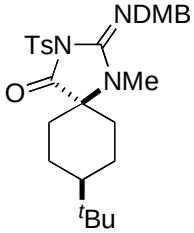
10

8-^{t}Bu-2-(3,4-dimethoxybenzylamino)-1-methyl-1,3-diazaspiro[4.5]dec-2-en-4-one (11): To a solution of 8-^{t}Bu-1-methyl-2-(methylthio)-1,3-diazaspiro[4.5]dec-2-en-4-one (**10**) (31 mg, 0.12 mmol) in MeCN (3 mL) was added $DMBNH_2$ (39 µL, 0.24 mmol) and $HgCl_2$ (35 mg, 0.13 mmol). The resulting mixture was heated to 80 ^{o}C in the microwave reactor for 3 h. After cooling to 23 ^{o}C, the solvent was removed and the resulting residue was purified by flash column chromatography (EtOAc) to afford the desired product as a colorless oil (42 mg, 90%): R_f 0.2 (EtOAc); IR (thin film) 3002, 2946, 1690, 1610 cm^{-1}; ^{1}HNMR (500 MHz, $CDCl_3$) δ 6.90-6.84 (m, 2H), 6.75 (d, *J* = 17.5 Hz, 1H), 6.18 (br, 1H), 4.57 (d, *J* = 9.0 Hz, 2H), 3.82, (s, 3H), 3.80 (s, 3H), 3.08 (s, 3H), 1.92, (dt, *J* = 17.5, 8.5 Hz, 2H), 1.82-1.66 (m, 4H), 1.42-1.12 (m, 3H), 0.85 (s, 9H); ^{13}CNMR (125 MHz, $CDCl_3$) δ 191.3, 168.1, 148.9, 148.5, 130.7, 120.3, 111.4, 111.0, 66.8, 55.8, 55.7, 46.8, 46.0, 33.7, 32.4, 30.5, 27.3, 22.9; ESI HRMS calcd for $C_{22}H_{34}N_3O_3$ [M+H] 388.2600, found 388.2557.



11

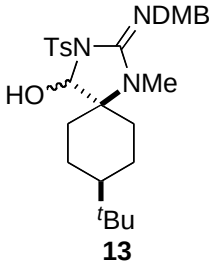
8-^{t}Bu-2-(3,4-dimethoxybenzylimino)-1-methyl-3-tosyl-1,3-diazaspiro[4.5]decan-4-one (12): NaH (60% in mineral oil, 10 mg, 0.24 mmol) was added to a solution of 8-^{t}Bu-2-(3,4-dimethoxybenzylamino)-1-methyl-1,3-diazaspiro [4.5]dec-2-en-4-one (**11**) (46 mg, 0.12 mmol). The resulting mixture was stirred at 23 ^{o}C for 30 min and TsCl (45 mg, 0.24 mmol) was added. The resulting mixture was stirred for 24 h and TLC showed no starting material left. Saturated NH_4Cl was added and the aqueous phase was extracted with CH_2Cl_2. The combined organic phase was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography (50% EtOAc/hexanes) to afford the desired product as a white foam (42 mg, 63%): R_f 0.35 (30:70, EtOAc:hexanes); IR (thin film) 2960, 1716 cm^{-1}; ^{1}HNMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.0 Hz, 2H),



12

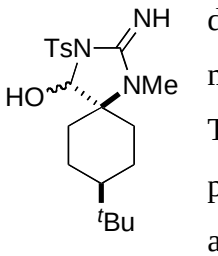
7.36 (d, *J* = 8.0 Hz, 2H), 6.87-6.83 (m, 2H), 6.75 (d, *J* = 8.5 Hz, 1H), 4.40 (s, 2H), 3.84 (s, 3H), 3.81 (s, 3H), 3.23 (s, 3H), 2.45 (s, 3H); 1.88 (dt, *J* = 15.0, 5.0 Hz, 2H), 1.82-1.72 (m, 3H), 1.30-1.12 (m, 4H), 0.85 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.8, 170.2, 149.3, 149.0, 145.5, 133.8, 130.2, 128.6, 126.3, 122.2, 112.2, 110.9, 69.1, 56.1, 56.0, 53.4, 45.9, 33.7, 33.4, 32.6, 27.4, 23.0, 21.9; ESI HRMS calcd for $C_{29}H_{40}N_3O_5S$ 542.2689, found 542.2681.

8-tert-butyl-2-(3,4-dimethoxybenzylimino)-1-methyl-3-tosyl-1,3-diazaspiro[4.5]decan-4-ol (13): To a solution of 8-^{t}Bu-2-(3,4-dimethoxybenzylimino)-1-methyl-3-tosyl-1,3-diazaspiro[4.5]-decan-4-one (**12**) (70 mg, 0.14 mmol) in CH_2Cl_2 (5 mL) at -78 ^{o}C was added DIBAL-H (1.0 M solution in CH_2Cl_2, 0.21 mL) dropwise. The reaction was stirred at -78 ^{o}C for 4 h. Sodium potassium tartrate solution (1M, 5 mL) was added and the reaction was warmed to 23 ^{o}C and stirred overnight. The aqueous phase was extracted with EtOAc and the combined organic phase was dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (2% Et_3N in EtOAc) afford desired product as a white foam (53 mg, 75%): R_f 0.44 (2:98, Et_3N:EtOAc); IR (thin film) 3179, 2954, 1590 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.0 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 6.89 (s, 1H), 6.85 (dd, *J* = 8.0, 1.3 Hz, 1H), 6.76 (d, *J* = 8.0 Hz, 1H), 4.58 (s, 1H), 4.53 (br, 1H), 4.29 (br, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 2.96 (s, 3H), 2.05 (s, 3H), 1.76-1.58 (m, 4H), 1.43-1.34 (m, 1H), 1.26-1.18 (m, 3H), 1.08-1.02 (m, 1H), 0.86 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.7, 149.1, 149.0, 144.7, 134.5, 129.9, 128.5, 127.4, 122.0, 112.3, 110.8, 94.9, 65.3, 56.1, 56.0, 53.5, 46.8, 37.6, 32.7, 32.6, 27.6, 26.2, 23.5, 23.0, 21.9; ESI HRMS calcd for $C_{29}H_{42}N_3O_5S$ [M+H] 544.2845, found 544.2839.



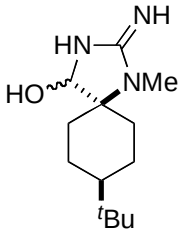
13

8-^{t}Bu-2-imino-1-methyl-3-tosyl-1,3-diazaspiro[4.5]decan-4-ol: To a solution of 8-^{t}Bu-2-(3,4-dimethoxybenzylimino)-1-methyl-3-tosyl-1,3-diazaspiro[4.5]decan-4-ol (**13**) (54 mg, 0.1 mmoL) in CH_2Cl_2 (5 mL) was added TFA (6.0 mL) and the reaction was stirred for 24 h. The reaction was diluted with CH_2Cl_2 and washed with aqueous $NaHCO_3$. The aqueous phase was extracted with CH_2Cl_2. The combined organic phase was dried over Na_2SO_4 and concentrated. The residue was subjected to flash column chromatography (70:30, EtOAc:hexanes) to afford the hemiaminal as a white foam (36 mg, 85%): R_f 0.35 (1:1, hexanes:EtOAc); IR (this film) 3390, 2951, 1587 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* =8.0 Hz, 2H), 7.61 (s, 1H), 7.23 (d, *J* = 8.0 Hz, 2H), 4.75 (d, *J* = 8.0 Hz, 1H), 3.86 (d, *J* = 7.5 Hz, 1H), 3.04 (s, 3H), 2.39 (s, 3H), 2.02-1.96 (m, 1H), 1.90-1.76 (m, 3H), 1.70-1.64 (m, 1H), 1.54-1.30 (m, 2H), 1.08 (apparent tt, *J* = 12.0, 4.0 Hz, 1H), 0.86 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.6, 142.3, 141.0, 129.5, 126.3, 86.4, 63.7, 46.1, 36.3, 32.8, 30.5, 27.7, 26.9, 23.2, 23.0, 21.7; ESI HRMS calcd for $C_{20}H_{32}N_3O_3S$ [M+H] 394.2164,



found 394.2161.

8-^{t}Bu-2-imino-1-methyl-1,3-diazaspiro[4.5]decan-4-ol (4): To a solution of 8-^{t}Bu-2-imino-1-methyl-3-tosyl-1,3-diazaspiro[4.5]decan-4-ol (21 mg, 0.05 mmol) in THF (5 mL) at -78 ^{o}C was added sodium naphthalenide (0.1 M in THF, 2.0 mol) and the reaction was stirred at -78 ^{o}C for 6 h. The reaction was quenched by aqueous HCl (0.1 M, 3 mL) and THF was removed under reduced pressure. The resulting mixture was washed with Et_2O and concentrated. The residue was treated with $CHCl_3$ (20 mL) and pass through a layer of celite to remove the inorganic salt. $CHCl_3$ was removed in vacuo to afford the desired product as a white foam (8.0 mg, 70%): IR (thin film) 3301, 2951, 1675 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 4.51 (s, 1H), 2.98 (s, 3H), 1.97 (qq, *J* = 13.0, 3.0 Hz, 2H), 1.87-1.83 (m, 1H), 1.78-1.71 (m, 2H), 1.59, (dq, *J* = 13.5, 4.0 Hz, 1H), 1.50-1.35 (m, 2H), 1.15 (apparent tt, *J* = 11.5, 4.0 Hz, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 163.4, 86.6, 64.6, 48.6, 38.8, 34.3, 30.4, 29.8, 28.8, 25.4, 25.1; ESI HRMS calcd for $C_{13}H_{26}N_3O$ [M+H] 240.2076, found 240.2078.



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