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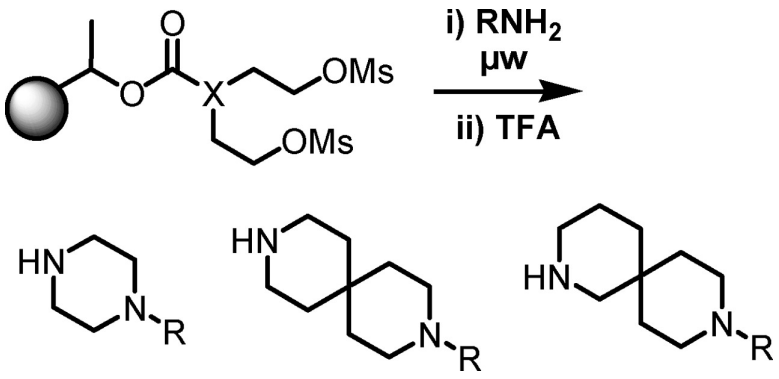

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Annulation of Primary Amines to Piperazines and Diazaspirocycles Utilizing α-Methyl Benzyl Resin

Calum Macleod,*,† Blanca I. Martinez-Teipel, William M. Barker, and Roland E. Dolle*

Department of Chemistry, Adolor Corporation, 700 Pennsylvania Drive, Exton, Pennsylvania 19341

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The microwave-assisted solid-phase synthesis of piperazines, 3,9-diazaspiro[5.5]undecanes and 2,9-diazaspiro-[5.5]undecanes is reported. The synthesis relies on the direct annulation of primary amines with resin-bound bismesylates **12**, **17**, and **22**. Critical to the success of this chemistry was the development of α-methyl benzyl carbamate resin linker. This resin permits the cleavage of the heterocycles under mildly acidic conditions, free of contaminating linker-derived N-alkylated byproducts.

Amine derivatization, widely employed in high-throughput synthesis, is highly effective in establishing nascent structure−activity relationships in biologically active leads. Standard protocols and reagents described to date yield the familiar acyclic derivatives, including amides, sulfonamides, ureas, and higher order amines (via reductive amination). In contrast, analogous "off-the-shelf" reagents to carry out amine annulations, invaluable in creating heterocyclic ring systems found in drug substances, are comparatively less common. We recently reported on a conceptually new family of annulation reagents for this purpose, dubbed SPAn reagents.[1] The reaction manifold, adapted to semiautomated library production, employed alkylation−intramolecular acylation of resin-bound haloalkyl esters with primary amines to give six- and seven-membered ring heterocycles in a single step. In an effort to expand our SPAn technology platform, we sought to develop a robust solid-phase synthesis (SPS) of piperazines and related diazaspirocycles via amine annulation chemistry. This approach, potentially taking advantage of the >30 000 commercially available primary amines, involves construction of aza-annulated products utilizing a bis-electrophilic resin followed by cleavage.

The piperazine motif is a pharmacophore commonly found in compounds of biological interest.[2] For example, it is present in a potent inhibitor of the plasminogen activator inhibitor-1 (PAI-1);[2a] potential antipsychotic agents with high affinity for dopamine and serotonin receptors;[2b] a 5-HT_3 antagonist;[2c] and in the potent, selective κ-opioid receptor agonist GR89696.[2d] Piperazines can be considered privileged substructures because ligands containing the piperazine core are capable of binding to multiple receptors with high affinity.[3] 3,9-Diazaspiro[5.5]undecanes have been identified as neuroleptic agents,[4a] and more recently as potent and specific antagonists of the nonpeptide glycoprotein (GP) IIb-IIIa,[4b] associated with platelet aggregation.

Previous strategies for the SPS of substituted piperazines have relied almost entirely on the functionalization of an immobilized piperazine ring.[5] The solid-phase construction of the piperazine ring itself has been reported, albeit by a borane-mediated oxamide reduction of the corresponding diketopiperazines.[6] There have been no reports detailing the SPS of diazaspiro[5.5]undecane scaffolds.

Numerous methods exist for anchoring amines to the solid phase. Among these, amine linkers based on common protecting groups, including benzyl,[7] THP,[8a,b] and the benzyl[9] and *t*-Boc carbamates,[10] have been developed. Herein, we report the development of a novel amine resin-linkage strategy which may prove superior to conventional amine linkers for the SPS of certain scaffolds where *N*-nucleophiles are released. This new linker strategy was crucial to the preparation of the SPAn reagents and successful amine annulation affording piperazines, 3,9-diazaspiro[5.5]undecanes, and 2,9-diazaspiro[5.5]undecanes.

Results and Discussion

We investigated the synthesis of mono-N-substituted piperazines via the route outlined in Scheme 1. Activated carbonate resin **1** was formed from Wang resin by a literature procedure.[5] Reaction of resin **1** with diethanolamine, at 60 °C in DMF, yielded carbamate resin **2**. Reaction completion was confirmed by conducting a small-scale TFA-cleavage reaction of resins **2**. Examination of the ^{1}H NMR spectrum showed that the crude product lacked signals from 4-nitrophenol [($CDCl_3$) δ 6.90 (2H, d) and 8.10 (2H, d)]. Bismesylation of diol **2** yielded SPAn reagent **3**. Conditions for the construction of the piperazine core via the primary amine-mediated annulation of SPAn reagent **3** (**3** + amine → **4**) were then investigated. Conventional heating (15−20 h) using a wide range of solvents and bases gave unsatisfactory results. Amino alcohols **5**[11a] and hydroxybenzylated byproducts **6**[11b] were significant contaminants observed upon TFA cleavage (50% TFA in DCM). Employing the dichloro variant of resin **3** (even under in situ Finkelstein conditions with KI in NMP) gave similar results. Fortunately, the use

* To whom correspondence should be addressed. Phone: 484.595.1024. Fax: 484.595.1551. E-mail: rdolle@adolor.com.

† Postdoctoral Fellow, 2003-2004. Current address: Argenta Discovery LtD., U.K. E-mail: calum.macleod@argentadiscovery.com.

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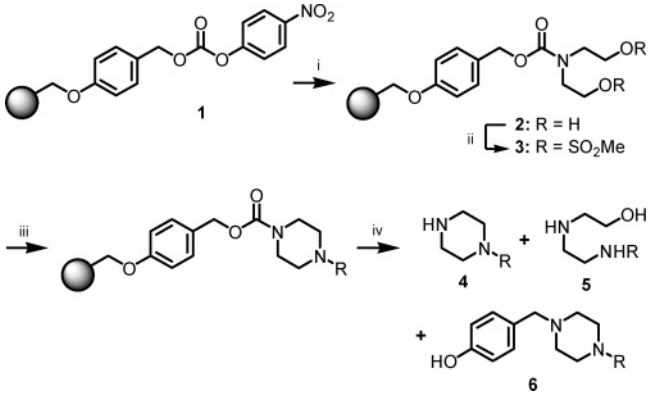
Scheme 1. Synthesis of Piperazines on Wang Resin[a]



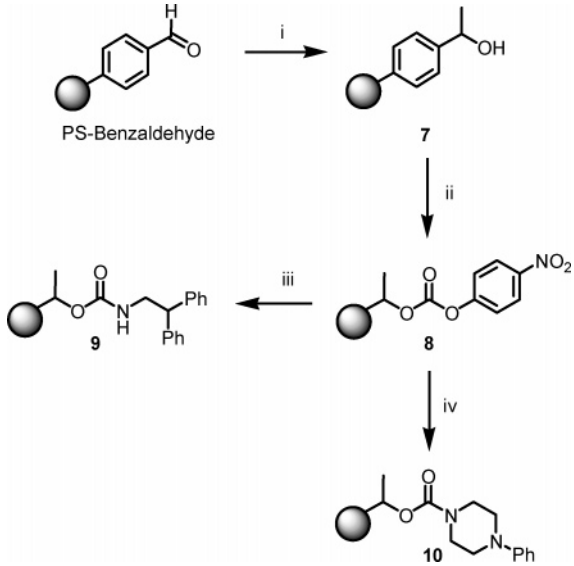
[a] Reagents and conditions: (i) diethanolamine (5 equiv), DMF, DIEA, DMAP, 70 °C, 12 h; (ii) $MeSO_2Cl$ (5 equiv), DCM, TEA, DMAP, 0−25 °C, 12 h; (iii) RNH_2 (10 equiv), NMP, DIEA, μw 160 °C, 30 min; (iv) TFA−DCM 1:1, 25 °C, 0.5−1 h.

of microwave irradiation with NMP as solvent aided piperazine formation, because amino alcohols **5** were no longer observed in significant quantity by LC/MS and ^{1}H NMR analysis upon resin cleavage; however, piperazines **4** were still contaminated with byproducts **6** in the crude cleavage mixture. Hydroxybenzylation of Wang resin-cleavage products has been previously reported.[12a,b] Attempts to suppress the formation of **6** employing HCl[10] instead of TFA and also by utilizing various scavenger cleavage cocktails (including H_2O, PhSMe, and *i*-Pr_3SiH mixtures) were unsuccessful.

Contaminants **6** were presumed to originate from an anomalous cleavage, albeit at a low level, of the benzyl ether bond through which *p*-hydroxybenzyl alcohol is attached to Merrifield resin. Therefore, a more robust resin linker was sought, one that did not contain a benzyl ether bond, potentially providing for clean resin cleavage of piperazines under acidic conditions. A literature report detailing the acid lability of esters derived from an α-methyl benzyl linkage[13] prompted an investigation of the α-methyl benzyl (AMB) carbamate analogues. Because this resin is derived from PS-benzaldehyde, there is no benzyl ether bond to break leading to possible N-alkylated byproducts. The AMB resin was prepared by treating PS-benzaldehyde (Argonaut) with methylmagnesium bromide in diethyl ether/THF. Complete reaction to alcohol **7** was confirmed by a negative result for the on-bead DNP test for aldehyde[14] (Scheme 2). Formation of the secondary carbonate **8** was achieved following treatment of resin **7** with 4-nitrophenyl chloroformate in THF, which required heating overnight. Subsequent reaction of the activated carbonate **8** with 2,2-diphenylethylamine or 1-phenylpiperazine furnished the primary carbamate **9** and secondary carbamate **10**, respectively. Loadings of resins **8**−**10** were determined by N elemental analysis. To our satisfaction, clean and efficient cleavage of resins **9** and **10** were achieved employing a range of TFA−DCM solutions (Table 1). Notably, a relatively mild 10% TFA in DCM solution appears adequate for cleavage from this linker.

To apply this linker in the SPS of piperazines, we reacted AMB nitrophenyl carbonate resin **8** with diethanolamine to yield diol **11**, which in turn was bis-mesylated to yield SPAn reagent **12**. Elemental analysis for S, N, or both S and N determined the loadings of resins **11** and **12**. Cyclization of

Scheme 2. Synthesis of the AMB Carbamate Resin[a]



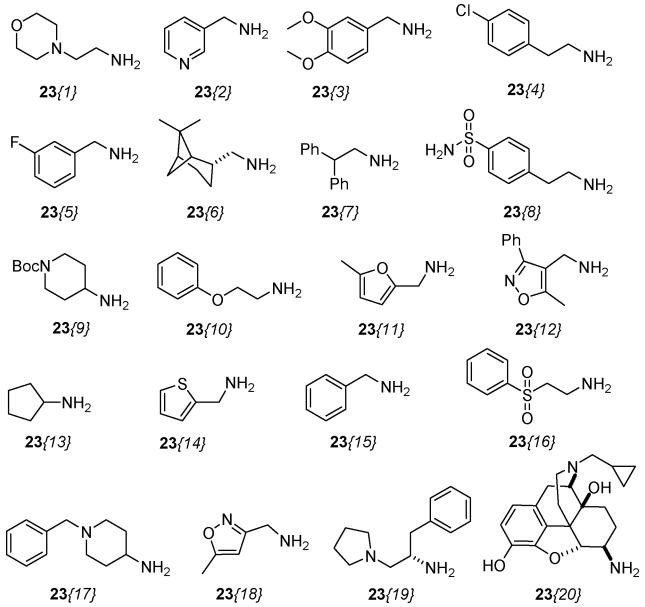
[a] Reagents and conditions: (i) MeMgBr (4.5 equiv), THF, 0−25 °C, 12 h; (ii) 4-nitrophenyl chloroformate (5 equiv), THF, NMM, DMAP, 60 °C, 12 h; (iii) $Ph_2CHCH_2NH_2$ (5 equiv), DMF, DIEA, 70 °C, 12 h; (iv) 1-phenylpiperazine (5 equiv), DMF, DIEA, 70 °C, 12 h.

Table 1. Yields for TFA Cleavage of Carbamates **9** and **10**[a]

carbamate	yield for resin cleavage % TFA in DCM			
	50%	25%	10%	5%
9	88	88	82	60
10	84	80	79	40

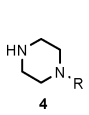
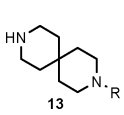
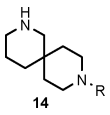
[a] The yields are based on the loading of resins **9** and **10** and are calculated for 2,2-diphenylethylamine/TFA and 1-phenylpiperazine 2/TFA, respectively.

Chart 1. Amine Inputs **23**{*1*−*20*}



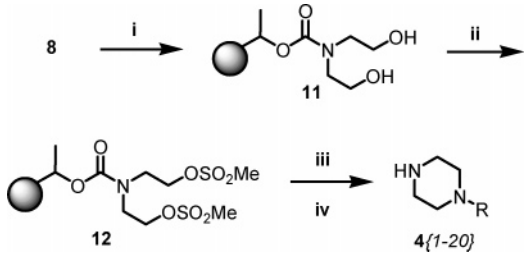
resin **12** with a set of 20 primary amines **23**{*1*−*20*} (Chart 1) was achieved employing the microwave irradiation-mediated cyclization conditions in NMP as the preferred solvent. The Milestone CombiChem Rotor (96-well format) was employed for the reactions, which were executed on a 50-μmol scale. Resin transfer (to a 96-well Unifilter filtration

Table 2. Purity and Yields of Library Products

	 4	 13	 14	
amine **23**	% purity **4**[a]	% purity **13**[b]	% purity **14**[a]	% yield **14**[c]
{*1*}	100	99	100	68[d]
{*2*}	94	98	89	79
{*3*}	98	95	90	73
{*4*}	99	100	92	75
{*5*}	97	86	80	66
{*6*}	98	100	84	64
{*7*}	97	100	92	71
{*8*}	97	100	90	63
{*9*}	95	*e*	77	54
{*10*}	98	100	91	70
{*11*}	80	69	83	73
{*12*}	94	100	79	68
{*13*}	98	98	85	75
{*14*}	97	95	82	63
{*15*}	93	100	78	69
{*16*}	89	92	38	51
{*17*}	96	99	79	58[d]
{*18*}	94	99	81	72
{*19*}	80	*e*	68	42[d]
{*20*}	82	100	70	58[d]

[a] Crude purity measured by ELSD. [b] Purified by mass-directed prep HPLC and purity measured by ELSD. [c] Yields based on loading of resin **22** and calculated for bis-TFA salt. [d] Yield based on loading of resin **22** and calculated for tris-TFA salt. [e] Sample lost during prep HPLC.

Scheme 3. Synthesis of Piperazines Employing the α-Methylbenzyl Carbamate Resin[a]

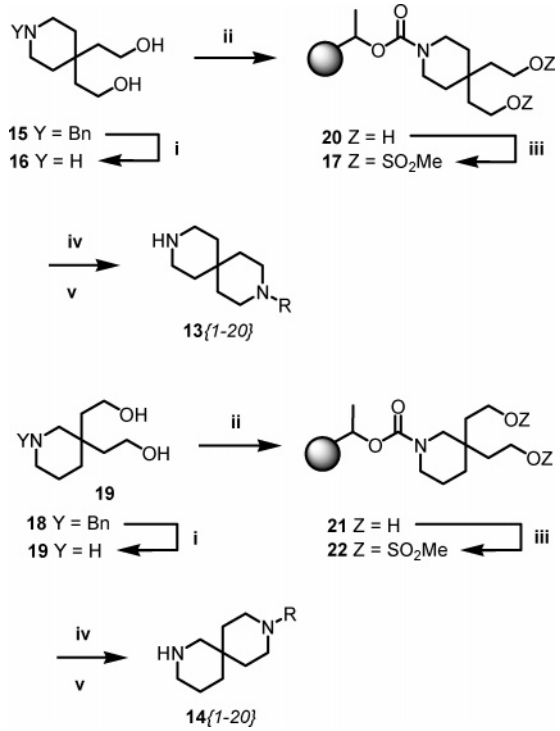


[a] Reagents and conditions: (i) diethanolamine (5 equiv), DMF, DIEA, DMAP, 70 °C, 12 h; (ii) $MeSO_2Cl$ (5 equiv), DCM, TEA, DMAP, 0−25 °C, 12 h; (iii) RNH_2 (10 equiv), NMP, DIEA, μw 160 °C, 30 min; (iv) TFA/DCM (1:1), 1 h.

block) and resin washing were achieved using a Quadra 3 liquid handler. Cleavage was carried out with 50% TFA in DCM to yield the desired piperazines **4**{*1*−*20*} in high crude purity (Table 2) and *without* trace of any linker-derived byproducts **6**.

The same synthetic strategy was then applied to the syntheses of 3,9-diazaspiro[5.5]undecanes **13**{*1*−*20*} and 2,9-diazaspiro[5.5]undecanes **14**{*1*−*20*}. *N*-Benzylamine **15** was synthesized as previously reported[15] and then debenzylated to yield secondary amine **16**. Piperidine **16** was loaded onto resin, via reaction with resin **8** as above, and then bismesylation yielded the corresponding SPAn reagent **17** (Scheme 4). Cyclization with the same set of amines **23**{*1*−*20*}, followed by resin cleavage, yielded 3,9-diazaspiro-[5.5]undecanes **13**{*1*−*20*} (Table 2). The products in this case were slightly contaminated (∼10%) with amines **16**, the corresponding cyclic ethers, or both. Purification by mass-directed HPLC (see Experimental Section) gave products

Scheme 4. Synthesis of Diazaspiro[5.5]undecanes[a]



[a] Reagents and conditions: (i) Pd/C, cyclohexene, MeOH−H_2O, reflux, 12 h; (ii) resin **8** (0.2 equiv), DMF, DIEA, DMAP, 70 °C, 12 h; (iii) $MeSO_2Cl$ (5 equiv with respect to **8**), DCM, TEA, DMAP, 0−25 °C, 12 h; (iv) RNH_2 (10 equiv), NMP, DIEA, μw 160 °C, 30 min; (v) TFA/DCM (1:1), 1 h.

13{*1*−*20*} in high purity. Employing amine **18**[15] and following the same synthetic strategy, 2,9-diazaspiro[5.5]-undecanes **14**{*1*−*20*} were synthesized in high crude purity without the need for HPLC purification.

In conclusion, the microwave-assisted SPS of piperazines, 3,9-diazaspiro[5.5]undecanes, and 2,9-diazaspiro[5.5]undecanes has been described. This was achieved by the direct annulation of primary amines with resin-bound bismesylate reagents **12**, **17**, and **22**. Wang resin, originally employed in the reagents, was unsuitable as the acid-labile carbamate linker due to the formation of linker-derived N-alkylated byproducts **6** upon product release. On the basis of mechanistic considerations, a novel carbamate linkage strategy utilizing AMB resin was developed to circumvent this problem. The AMB−carbamate linker is efficiently cleaved under mild acidic reaction conditions, affording secondary amines without contamination. In addition to exploiting the normal benefits associated with SPS, advantages to this methodology include the prevention of possible contamination from oligomerization reactions while achieving site isolation through formation of the monosubstituted aza-annulated products. The ring NH in these products may, in turn, be subjected to derivatization. Bismesylates **12**, **17**, and **22** represent a new class of SPAn reagents, expanding the repertoire of streamlined primary amine annulation chemistry.[1]

Experimental Section

General Procedures. ^1H NMR spectra were recorded in 5-mm tubes on a 400-MHz Bruker spectrometer. ^1H NMR

spectra were referenced as follows: CD_3OD to MeOH (δ 3.35); $CDCl_3$ and $(CD_3)_2SO$ to TMS (δ 0.00). FT-IR were recorded at 4 cm^{-1} resolution on a spectrometer interfaced to an InspectIR attenuated total reflectance microscope with Si sampling optics. Solvents used were EM Science of OmniSolv distilled grade unless specified otherwise.

Mass-Directed HPLC Purification was performed on a Phenomenex LUNA C18(2) 7.8 × 100 mm, 5 μm, column at room temperature in a Gilson system equipped with a Gilson 215 liquid handler, a Gilson 819 injection module, three Gilson 306 pumps with 25-mL pump heads, a Gilson 155 dual wavelength UV/vis detector ($\lambda 1$ = 220 nm, $\lambda 2$ = 254 nm), and a Thermo-Finnigan AQA mass detector (ESI^+; cone, 30 V; capillary, 3.10 kV; probe at 350 °C; and scan range 150−700 amu) and Thermo-Finnigan Excaliber version 1.3 system control software. The injection volume was 0.500 mL, split flow 50 to 1, and flow rate was set at 10.5 mL/min of the following mobile phase gradient: 1% mobile phase A, 10% mobile phase B, 89% mobile phase C, hold for 1 min; proceed linearly to 15% mobile phase A, 10% mobile phase B, 75% mobile phase C over 2.50 min; proceed linearly to 15% mobile phase A, 65% mobile phase B, 20% mobile phase C over 3.50 min; hold for 3.5 min; reequilibrate to 1% mobile phase A, 10% mobile phase B, 89% mobile phase C (mobile phase A, 1% trifluoroacetic acid in HPLC grade water; mobile phase B, HPLC grade acetonitrile; mobile phase C, HPLC grade water). Fraction collector parameters: MS triggered with 10-mV trigger threshold.

LC/MS Analysis was performed on a SIELC Primesep 200, 2.1 × 100 mm column at 25 °C in a Waters Alliance 2795 equipped with a Waters 996 PDA (resolution, 4.8 nm; scan rate, 1 Hz) and a Waters ZQ2000 (electrospray with polarity +ve; cone, 35 V; capillary, 3.0 kV; scan time, 0.3 s for 150−800 amu). Flow rate was set at 0.7 mL/min of the following mobile phase gradient: 1% A, 10% B, 89% C for 1.0 min; to 15% A, 10% B, 75% B in 2.50 min; to 15% A, 65% B, 20% B in 3.50 min; hold for 3.5 min; reequilibrate to 1% A, 10% B, 89% C (solution A, 1% TFA in HPLC grade water; solution B, HPLC grade acetonitrile; solution C, HPLC grade water).

The Following Abbreviations are used: DCM = dichloromethane, DIEA = diisopropylamine, DMF = *N*,*N*-dimethylformamide, DMAP = *N*,*N*-dimethylamino pyridine, DMSO = dimethyl sulfoxide, EI-MS = electron ionization mass spectrometry, ELSD = evaporative light scattering detection, FT-IR = Fourier transform infrared spectroscopy, HPLC = high performance liquid chromatography, LC/MS = liquid chromatography mass spectroscopy, NMM = *N*-methyl morpholine, NMP = *N*-methyl-2-pyrrolidinone, TEA = triethylamine, TFA = trifluoroacetic acid, THF = tetrahydrofuran, and TMS = tetramethylsilane.

Wang Carbamate Resin 2. In a 250-mL, round-bottomed flask, the Wang nitrocarbonate resin **1**[5] (3.76 g; 5.00 mmol; theoretical 1.33 mmol g^{-1}) was swollen in anhydrous DMF (125 mL). DIEA (17.5 mL; 100 mmol) and diethanolamine (4.8 mL; 50 mmol) were added at room temperature, and the reaction mixture was then heated to 60 °C with stirring overnight. The solvent was removed by vacuum filtration, and the resin was washed with DMF (10 × 50 mL). The resin was then subjected to a second coupling performed in a fashion analogous to that described above. The solvent was removed by vacuum filtration, and the resin was washed with DMF (5 × 20 mL), DCM/MeOH [alternate (5 × 20 mL)] and then dried overnight in a vacuum oven at ambient temperature. FT-IR: 1685 cm^{-1} (C═O). A small-scale cleavage reaction (50% TFA−DCM; 30 min; followed by evaporation of the DCM washings) confirmed coupling was complete because 4-nitrophenol was not observed in the crude ^1H NMR spectrum.

Dimesylate Resin 3. In a 30-mL, glass Radley's reactor tube, the carbamate **2**[5] (0.72 g; 1.00 mmol; assume 1.39 mmol g^{-1}) was swollen in anhydrous DCM (25 mL). TEA (2.1 mL; 15.0 mmol) and DMAP (0.012 g; 0.10 mmol) were added, and the reaction mixture was cooled using an ice bath. Methanesulfonyl chloride (0.8 mL; 10.0 mmol) was added dropwise at 0 °C, and a vigorous reaction resulted. The reaction mixture was allowed to warm to room temperature with gentle stirring overnight. After this time, the solvent was removed by vacuum filtration, and the resin was washed with THF (5 × 20 mL) and DCM/diethyl ether [alternate (5 × 20 mL)] and then dried overnight in a vacuum oven at ambient temperature.

Alcohol Resin 7. In a 250-mL, round-bottomed flask, PS-benzaldehyde resin (Argonaut 1.25 mmol g^{-1}; 8.77 g; 11.0 mmol)[16] was swollen in anhydrous THF (100 mL). The flask was then purged with nitrogen and cooled using an ice bath. Methylmagnesium bromide (3.0 M in diethyl ether; 16.7 mL; 50.0 mmol) was then added carefully, and the reaction mixture was allowed to warm to room temperature with gentle stirring for 18 h. A small portion of the resin was tested under the solid-phase DNP test[14] to ensure complete reaction. The solvent was removed by vacuum filtration [filtrate quenched into water (200 mL)]. The resin was washed with THF (5 × 50 mL), water (3 × 50 mL), DMF (3 × 50 mL), MeOH/DCM (alternate 5 × 50 mL), and THF (1 × 50 mL) and then dried overnight in a vacuum oven at ambient temperature.

Carbonate Resin 8. In a 500-mL, round-bottomed flask, the alcohol resin **7** (11.0 mmol) was swollen in anhydrous THF (200 mL). NMM (11.0 mL; 100 mmol), DMAP (50 mg; 0.41 mmol), and then 4-nitrophenyl chloroformate (10.07 g; 50.0 mmol) were added at room temperature. The reaction mixture was then allowed to stir gently for 30 min before transferring the reaction flask to an oil bath maintained at 60 °C, with gentle stirring continued for 44 h. The solvent was removed by vacuum filtration, and the resin was washed with THF (3 × 50 mL); DMF (5 × 50 mL); THF (3 × 50 mL); and finally, with DCM (3 × 50 mL). The resin was then retreated for 15 h and washed as above before drying in a vacuum oven overnight at ambient temperature. Microanalysis: found, N 1.60% (1.16 mmol g^{-1}).

Carbamate Resins 9 and 10 General Procedure. In a 30-mL, glass Radley's reactor tube, the nitrocarbonate resin 8 (0.53 g; 0.61 mmol) was swollen in anhydrous DMF (25 mL). DIEA (0.9 mL; 5.14 mmol), DMAP (0.05 g; 0.41 mmol), and then amine (2.50 mmol) were added at room temperature, and the reaction mixture was then heated to 60 °C on a Radley's carousel with moderate stirring for 15 h.

The solvent was removed by vacuum filtration, and the resin was washed with DMF (5 × 50 mL), THF (5 × 50 mL), and DCM (5 × 50 mL) and then dried overnight in a vacuum oven at ambient temperature. A small-scale cleavage reaction (50% TFA−DCM; 30 min; followed by evaporation of the DCM washings) confirmed coupling was complete because 4-nitrophenol was not observed in the crude ^{1}H NMR spectrum.

Carbamate Resin 9. The general procedure employing 2,2-diphenylethylamine (0.50 g; 2.50 mmol) yielded the desired resin **9**. FT-IR: 1718 cm^{-1} (C═O). Microanalysis: found, N 1.56% (1.11 mmol g^{-1}).

Carbamate Resin 10. The general procedure employing 1-phenylpiperazine (0.38 mL; 2.50 mmol) yielded the desired resin **10**. FT-IR: 1698 cm^{-1} (C═O). Microanalysis: found, N 3.09% (1.10 mmol g^{-1}).

Carbamate Resin Cleavage General Procedure. TFA (50% in DCM, 1 mL), was added to resin **9** (55.8 mg, 1.11 mmol g^{-1}, 54.3 μmol) or resin **10** (54.0 mg, 1.10 mmol g^{-1}, 59.4 μmol) in an Isolute SPE fritted column and placed on an orbital shaker for 1 h. After this time, the resin was filtered and washed with DCM (3 × 1 mL). The DCM washings and filtrate were combined and concentrated under nitrogen before being transferred to a vacuum oven and further dried to constant weight.

Cleavage of Carbamate Resin 9. Employing TFA (50% in DCM, 1 mL) yielded 2,2-diphenylethylamine·TFA as a white solid (16.9 mg, 54.3 μmol, 88%); employing TFA (25% in DCM, 1 mL) yielded 2,2-diphenylethylamine·TFA as a white solid (17.0 mg, 54.3 μmol, 88%); employing TFA (10% in DCM, 1 mL) yielded 2,2-diphenylethylamine·TFA as a white solid (15.8 mg, 50.7 μmol, 82%); employing TFA (5% in DCM, 1 mL) yielded 2,2-diphenylethylamine·TFA as a white solid (11.5 mg, 36.9 μmol, 60%).

Cleavage of Carbamate Resin 10. Employing TFA (50% in DCM, 1 mL) yielded 1-phenylpiperazine 2·TFA as a white solid (19.5 mg, 49.8 μmol, 84%); employing TFA (25% in DCM, 1 mL) yielded 1-phenylpiperazine 2·TFA as a white solid (18.6 mg, 47.5 μmol, 80%); employing TFA (10% in DCM, 1 mL) yielded 1-phenylpiperazine 2·TFA as a white solid (18.3 mg, 46.9 μmol, 79%); employing TFA (5% in DCM, 1 mL) yielded 1-phenylpiperazine 2·TFA as a white solid (9.30 mg, 23.8 μmol, 40%).

Carbamate Resin 11. In a 250-mL, round-bottomed flask, the nitrocarbonate resin **8** (5.30 g; 6.15 mmol) was swollen in anhydrous DMF (150 mL). DIEA (9.00 mL; 51.4 mmol), DMAP (0.30 g; 2.46 mmol), and then diethanolamine (2.4 mL; 25.0 mmol) were added at room temperature, and the reaction mixture was then heated to 60 °C with moderate stirring for 72 h. The solvent was removed by vacuum filtration, and the resin was washed with DMF (5 × 50 mL), THF (5 × 50 mL), and DCM/MeOH [alternate (5 × 50 mL)] and then dried overnight in a vacuum oven at ambient temperature. FT-IR: 1683 cm^{-1} (C═O). Microanalysis: found, N 1.23% (1.11 mmol g^{-1}). A small-scale cleavage reaction (50% TFA−DCM; 30 min; followed by evaporation of the DCM washings) confirmed coupling was complete because 4-nitrophenol was not observed in the crude ^{1}H NMR spectrum.

Dimesylate Resin 12. In a 30-mL, glass Radley's reactor tube, the carbamate resin **11** (2.05 g; 2.52 mmol) was swollen in anhydrous DCM (35 mL). TEA (4.0 mL; 28.7 mmol) and then DMAP (0.10 g; 0.82 mmol) were added, and the reaction mixture was cooled using an ice bath. Methanesulfonyl chloride (1.6 mL; 20.0 mmol) was added dropwise at 0 °C, and a vigorous reaction resulted. The reaction mixture was allowed to warm to room temperature with gentle stirring overnight. After this time, the solvent was removed by vacuum filtration, and the resin was washed with DMSO (5 × 30 mL), THF (5 × 30 mL), and DCM/diethyl ether [alternate (5 × 30 mL)] and then dried overnight in a vacuum oven at ambient temperature. Microanalysis: found, N 1.40%; S 5.85% (0.78 mmol g^{-1} based on S analysis).

Amine 16. In a 500-mL, round-bottomed flask, amine **15**[15] (10.54 g; 40.0 mmol) was dissolved in MeOH (100 mL). Cyclohexene (100 mL) and then Pd/C (10% Pd on carbon, 50% H_2O by weight, 4.25 g; 0.20 mmol) were added and then heated under reflux overnight for 16 h. The reaction mixture was filtered through wet Celite, washing with MeOH/water, and then evaporated to dryness. This crude mixture was dried overnight in a vacuum oven at ambient temperature to yield amine **16** as an off-white solid (6.23 g, 90%): ^{1}H NMR (CD_3OD) δ 3.65−3.69 (4H, m), 2.85 (4H, t), 1.66−1.69 (4H, m), 2.50 (4H, t).

Amine 19. In a 500-mL, round-bottomed flask, amine **18**[15] (3.94 g; 15.0 mmol) was dissolved in MeOH (25 mL). Cyclohexene (25 mL) and then Pd/C (10% Pd on carbon, 50% H_2O by weight, 1.47 g; 0.07 mmol) were added and then heated under reflux overnight for 20 h. The same workup procedure as for amine **16** yielded amine **19** as a yellow oil (2.26 g, 87%): ^{1}H NMR [$(CD_3)_2SO$] δ 4.31 (1H, bs), 3.41−3.45 (4H, m), 2.74 (4H, t), 1.46 (4H, t), 1.36 (4H, t).

Carbamate Resin 20. In a 100-mL, round-bottomed flask, the nitrocarbonate resin **8** (2.62 g; 2.24 mmol) was swollen in anhydrous DMF (50 mL). DIEA (8.75 mL; 50.0 mmol) and then amine **16** (2.17 g; 12.5 mmol) were added at room temperature, and the reaction mixture was then heated to 60 °C with moderate stirring for 72 h. The solvent was removed by vacuum filtration, and the resin was washed with DMF (5 × 50 mL), THF (5 × 50 mL), and DCM/MeOH [alternate (5 × 50 mL)] and then dried overnight in a vacuum oven at ambient temperature. FT-IR: 1687 cm^{-1} (C═O). Microanalysis: found, N 1.51% (1.18 mmol g^{-1}). A small-scale cleavage reaction (50% TFA−DCM; 30 min; followed by evaporation of the DCM washings) confirmed coupling was complete because 4-nitrophenol was not observed in the crude ^{1}H NMR spectrum.

Dimesylate Resin 17. In a 30-mL, glass Radley's reactor tube, the carbamate resin **20** (2.19 g; 2.58 mmol) was swollen in anhydrous DCM (40 mL). DIEA (4.0 mL; 22.9 mmol) and then DMAP (0.10 g; 0.82 mmol) were added, and the reaction mixture was cooled using an ice bath. Methanesulfonyl chloride (1.6 mL; 20.0 mmol) was added dropwise at 0 °C, and a vigorous reaction resulted. The reaction mixture was allowed to warm to room temperature with gentle stirring overnight. After this time, the solvent was removed by vacuum filtration, and the resin was washed with

DMSO (5 × 30 mL), THF (5 × 30 mL), and DCM (5 × 30 mL) and then dried overnight in a vacuum oven at ambient temperature. Microanalysis: found, N 1.38%, S 5.60% (0.74 mmol g^{-1} based on S analysis).

Carbamate Resin 21. In a 100-mL, round-bottomed flask, the nitrocarbonate resin **8** (1.57 g; 1.50 mmol) was swollen in anhydrous DMF (30 mL). DIEA (5.25 mL; 30.0 mmol) and then amine **19** (1.30 g; 7.50 mmol) were added at room temperature, and the reaction mixture was then heated to 60 °C with moderate stirring for 44 h. The solvent was removed by vacuum filtration, and the resin was washed with DMF (5 × 50 mL), THF (5 × 50 mL), and DCM/MeOH [alternate (5 × 50 mL)] and then dried overnight in a vacuum oven at ambient temperature. FT-IR: 1697 cm^{-1} (C═O). Microanalysis: found, N 1.13% (0.81 mmol g^{-1}). A small-scale cleavage reaction (50% TFA−DCM; 30 min; followed by evaporation of the DCM washings) confirmed coupling was complete because 4-nitrophenol was not observed in the crude ^{1}H NMR spectrum.

Dimesylate Resin 22. In a 30-mL, glass Radley's reactor tube, the carbamate resin **21** (1.64 g; 1.32 mmol) was swollen in anhydrous DCM (30 mL). DIEA (3.0 mL; 17.1 mmol) and then DMAP (0.10 g; 0.82 mmol) were added, and the reaction mixture was cooled using an ice bath. Methanesulfonyl chloride (1.2 mL; 15.0 mmol) was added dropwise at 0 °C, and a vigorous reaction resulted. The reaction mixture was allowed to warm to room temperature with gentle stirring overnight. After this time, the solvent was removed by vacuum filtration, and the resin was washed with DMSO (5 × 30 mL), THF (5 × 30 mL), and DCM (5 × 30 mL) and then dried overnight in a vacuum oven at ambient temperature. Microanalysis: found, N 1.67%, S 4.10% (0.64 mmol g^{-1} based on S analysis).

General Microwave Cyclization Procedure. To mesylate resins **12**, **17**, or **22** (40.0−46.1 μmol) in 96-well Milestone CombiCHEM microwave reaction vials was added DIEA (175 μL, 1.0 mmol), followed by amines **23**{*1*−*20*} [NMP (1250 μmolmL^{-1}) stock solutions, 400 μL, 500 μmol]. The reaction vials were transferred to a Milestone Weflon 96-well plate, which was securely fitted to the Milestone CombiCHEM rotor and, in turn, inserted into the Milestone microwave (thermocouple must be inserted into the CombiCHEM plate at this point). A microwave program which involved heating so as to elevate the temperature from room temperature to 160 °C over 25 min and then maintain the temperature at 160 °C for 30 min, was applied. The reactions were allowed to cool to room temperature, NMP (500 μL) was added to each reaction vial, and the solvent was removed by filtration using a 96-well Unifilter filtration block. Each resin was washed with NMP (10 × 1 mL) and then MeOH/DCM (alternate 10 × 1 mL) and dried by vacuum suction.

Piperazine/Diazaspirocycle Resin Cleavage General Procedure. Added to the resin (contained in a septum bottom-sealed Unifilter filtration block) was TFA [(50% in DCM), 1 mL], and the block was allowed to stand for 1 h. After this time, the crude cleavage reactions were evaporated to dryness under nitrogen using a Micro-DS96 evaporator. The filtration block was removed from the septum and placed over a 2-mL, 96-well microtiter plate before washing each resin with MeOH/DCM (alternate 2 × 400 μL). The microtiter plate was transferred to an HT-12 evaporator (Genevac), and the samples were evaporated to dryness, yielding the crude products.

Piperazines 4. The general microwave cyclization procedure employing resin **12** (58.8 mg, 0.78 mmol g^{-1}, 45.9 μmol), followed by the general piperazine/diazaspirocycle resin cleavage procedure, yielded the desired piperazines TFA salts **4**{*1*−*20*}.

4-(2-Piperazin-1-yl)ethylmorpoline 3·TFA 4{*1*}. EI-MS *m*/*z* 200 $[M + H]^+$; LC_{area} (ELSD) = 100%.

1-(Pyridin-3-yl)methylpiperazine 2·TFA 4{*2*}. (19.9 mg, 51%), EI-MS *m*/*z* 178 $[M + H]^+$; LC_{area} (ELSD) = 94%.

1-(3,4-Dimethoxybenzyl)piperazine 2·TFA 4{*3*}. ^{1}H NMR (CD_3OD) δ 7.11 (1H, bs), 7.06 (2H, bs), 4.09 (2H, s), 3.89 (3H, s), 3.88 (3H, s), 3.39−3.44 (4H, m), 3.18−3.25 (4H, m); EI-MS *m*/*z* 237 $[M + H]^+$; LC_{area} (ELSD) = 98%.

1-[2-(4-Chlorophenyl)ethyl]piperazine 2·TFA 4{*4*}. (21.2 mg, 49%), ^{1}H NMR (CD_3OD) δ 7.34−7.39 (4H, m), 3.49 (4H, t), 3.32−3.37 (4H, m), 3.16−3.22 (2H, m), 2.99−3.03 (2H, m); EI-MS *m*/*z* 225 $[M + H]^+$; LC_{area} (ELSD) = 99%.

1-(3-Fluorobenzyl)piperazine 2·TFA 4{*5*}. EI-MS *m*/*z* 195 $[M + H]^+$; LC_{area} (ELSD) = 97%.

1-((1*R*,2*R*,5*R*)-6,6-Dimethylbicyclo[3.1.1]hept-2-ylmethyl)piperazine 2·TFA 4{*6*}. EI-MS *m*/*z* 223 $[M + H]^+$; LC_{area} (ELSD) = 98%.

1-(2,2-Diphenylethyl)piperazine 2·TFA 4{*7*}. (24.2 mg, 55%), ^{1}H NMR (CD_3OD) δ 7.32−7.42 (10H, m), 4.42 (1H, t), 3.45 (2H, d), 3.26−3.33 (4H, m), 3.07−3.12 (4H, m); EI-MS *m*/*z* 267 $[M + H]^+$; LC_{area} (ELSD) = 97%.

4-(2-Piperazin-1-yl)ethylbenzenesulfonamide 2·TFA 4{*8*}. ^{1}H NMR (CD_3OD) δ 7.89 (2H, d), 7.49 (2H, d), 3.45 (4H, t), 3.20−3.27 (4H, m), 3.05−3.17 (4H, m); EI-MS *m*/*z* 270 $[M + H]^+$; LC_{area} (ELSD) = 97%.

4-(Piperazin-1-yl)piperidine-1-carboxylic Acid *tert*-Butyl Ester 2·TFA 4{*9*}. EI-MS *m*/*z* 270 $[M + H]^+$; LC_{area} (ELSD) = 95%.

1-(2-Phenoxyethyl)piperazine 2·TFA 4{*10*}. ^{1}H NMR (CD_3OD) δ 7.33 (2H, t), 6.99−7.01 (3H, m), 4.31 (2H, t), 3.45−3.48 (4H, t), 3.30−3.35 (4H, m); EI-MS *m*/*z* 207 $[M + H]^+$; LC_{area} (ELSD) = 98%.

1-(5-Methylfuran-2-ylmethyl)piperazine 2·TFA 4{*11*}. ^{1}H NMR (CD_3OD) δ 6.41 (1H, d), 6.08 (1H, d), 4.02 (2H, s), 3.39−3.42 (4H, t), 3.10−3.14 (4H, t), 2.35 (3H, s); EI-MS *m*/*z* 181 $[M + H]^+$; LC_{area} (ELSD) = 80%.

1-(5-Methyl-3-phenylisoxazol-4-ylmethyl)-piperazine 2·TFA 4{*12*}. ^{1}H NMR (CD_3OD) δ 7.46 (1H, d), 7.11 (1H, d), 7.05 (1H, dd), 4.06 (2H, s), 3.32−3.36 (4H, m), 2.90−3.95 (4H, t); EI-MS *m*/*z* 258 $[M + H]^+$; LC_{area} (ELSD) = 94%.

1-Cyclopentylpiperazine 2·TFA 4{*13*}. EI-MS *m*/*z* 155 $[M + H]^+$; LC_{area} (ELSD) = 98%.

1-Thiophen-2-ylmethylpiperazine 2·TFA 4{*14*}. EI-MS *m*/*z* 183 $[M + H]^+$; LC_{area} (ELSD) = 97%.

1-((*S*)-1-Phenylethyl)piperazine 2·TFA 4{*15*}. EI-MS *m*/*z* 191 $[M + H]^+$; LC_{area} (ELSD) = 93%.

1-(2-Benzenesulfonylethyl)piperazine 2·TFA 4{*16*}. EI-MS *m/z* 255 $[M + H]^+$; LC_{area} (ELSD) = 89%.

1-(1-Benzylpiperidin-4-yl)piperazine 3·TFA 4{*17*}. EI-MS *m/z* 260 $[M + H]^+$; LC_{area} (ELSD) = 96%.

1-(5-Methylisoxazol-3-ylmethyl)piperazine 2·TFA 4{*18*}. EI-MS *m/z* 182 $[M + H]^+$; LC_{area} (ELSD) = 94%.

1-((*S*)-1-Benzyl-2-pyrrolidin-1-ylethyl)piperazine 3·TFA 4{*19*}. EI-MS *m/z* 274 $[M + H]^+$; LC_{area} (ELSD) = 80%.

4,5α-Epoxy-3-hydroxy-14*β*-hydroxy-6-*β*-(piperazin-1-yl)-17-(cyclopropylmethyl)morphinan 3·TFA 4{*20*}. EI-MS *m/z* 412 $[M + H]^+$; LC_{area} (ELSD) = 82%.

3,9-Diazaspirocycles 13. The general microwave cyclization procedure employing resin **17** (62.3 mg, 0.74 mmol g^{-1}, 46.1 μmol) followed by the general resin cleavage procedure [TFA (50% in DCM), 1 mL] yielded the desired 3,9-diazaspirocycles X·TFA **13**. The crude products were reconstituted in DMF (500 μL) and purified by mass-directed HPLC. The purified fractions were aliquoted for LC/MS analysis and evaporated to dryness using an HT-12 evaporator (Genevac) to yield the desired 3,9-diazaspirocycle TFA salts **13**{*1*−*20*}.

3-(2-Morpholin-4-ylethyl)-3,9-diazaspiro[5.5]undecane 3·TFA 13{*1*}. EI-MS *m/z* 268 $[M + H]^+$; LC_{area} (ELSD) = 99%.

3-(Pyridin-3-yl-methyl)-3,9-diazaspiro[5.5]undecane 2·TFA 13{*2*}. (4.9 mg, 23%),^{1}H NMR (CD_3OD) δ 8.74 (2H, m), 8.01 (1H, dt), 7.64 (1H, dt), 4.47 (2H, s), 3.17−3.41 (8H, m), 1.71−1.80 (4H, m), 1.96−2.04 (4H, m); EI-MS *m/z* 246 $[M + H]^+$; LC_{area} (ELSD) = 98%.

3-(3,4-Dimethoxybenzyl)-3,9-diazaspiro[5.5]undecane 2·TFA 13{*3*}. ^{1}H NMR (CD_3OD) δ 7.14 (1H, d), 7.05−7.10 (2H, m), 4.55 (2H, s), 3.90 (3H, s), 3.89 (3H, s), 3.23−3.39 (8H, m), 1.70−2.04 (8H, m); EI-MS *m/z* 305 $[M + H]^+$; LC_{area} (ELSD) = 95%.

3-[2-(4-Chlorophenyl)-ethyl]-3,9-diazaspiro[5.5]undecane 2·TFA 13{*4*}. (6.3 mg, 26%),^{1}H NMR (CD_3OD) δ 7.40 (2H, dd), 7.33 (2H, dd), 3.52−3.58 (2H, m), 3.17−3.45 (8H, m), 3.08−3.12 (2H, m), 1.75−2.75 (8H, m); EI-MS *m/z* 293 $[M + H]^+$; LC_{area} (ELSD) = 100%.

3-(3-Fluorobenzyl)-3,9-diazaspiro[5.5]undecane 2·TFA 13{*5*}. ^{1}H NMR (CD_3OD) δ 7.69−7.75 (1H, m), 7.44−7.57 (3H, m), 4.55 (2H, s), 3.28−3.65 (8H, m), 1.76−2.37 (8H, m); EI-MS *m/z* 263 $[M + H]^+$; LC_{area} (ELSD) = 86%.

3-((1*R*,2*R*,5*R*)-6,6-Dimethyl-bicyclo[3.1.1]hept-2-ylmethyl)-3,9-diazaspiro[5.5]undecane 2·TFA 13{*6*}. EI-MS *m/z* 291 $[M + H]^+$; LC_{area} (ELSD) = 100%.

3-(2,2-Diphenylethyl)-3,9-diazaspiro[5.5]undecane 2·TFA 13{*7*}. (4.3 mg, 17%), ^{1}H NMR (CD_3OD) δ 7.38−7.47 (8H, m), 7.29−7.33 (2H, m), 4.61 (1H, t), 4.00 (2H, d), 3.47−3.50 (2H, m), 3.21−3.36 (6H, m), 1.92−1.98 (4H, m), 1.68−1.76 (4H, m); EI-MS *m/z* 335 $[M + H]^+$; LC_{area} (ELSD) = 100%.

4-[2-(3,9-Diazaspiro[5.5]undec-3-yl)ethyl]benzenesulfonamide 2·TFA 13{*8*}. ^{1}H NMR (CD_3OD) δ 7.92 (2H, d), 7.52 (2H, d), 3.59−3.66 (2H, m), 3.44−3.47 (2H, m), 3.18−3.36 (8H, m), 1.90−2.15 (4H, m), 1.72−1.86 (4H, m); EI-MS *m/z* 338 $[M + H]^+$; LC_{area} (ELSD) = 100%.

3-(2-Phenoxyethyl)-3,9-diazaspiro[5.5]undecane 2·TFA 13{*10*}. ^{1}H NMR (CD_3OD) δ 7.36 (2H, t), 7.03−7.07 (3H, m), 4.41 (2H, t), 3.57−3.70 (4H, m), 3.24−3.34 (6H, m), 1.68−2.15 (8H, m); EI-MS *m/z* 275 $[M + H]^+$; LC_{area} (ELSD) = 100%.

3-(5-Methylfuran-2-ylmethyl)-3,9-diazaspiro[5.5]undecane 2·TFA 13{*11*}. ^{1}H NMR (CD_3OD) δ 6.61 (1H, d), 6.17 (1H, d), 4.38 (1H, s), 3.13−3.27 (8H, m), 2.36 (3H, s), 1.66−2.14 (8H, m); EI-MS *m/z* 249 $[M + H]^+$; LC_{area} (ELSD) = 69%.

3-(5-Methyl-3-phenylisoxazol-4-ylmethyl)-3,9-diazaspiro-[5.5]undecane 2·TFA 13{*12*}. ^{1}H NMR (CD_3OD) δ 7.67−7.71 (2H, m), 7.60−7.64 (3H, m), 4.44 (2H, s), 3.84−3.28 (8H, m), 2.66 (3H, s), 1.48−1.96 (8H, m); EI-MS *m/z* 326 $[M + H]^+$; LC_{area} (ELSD) = 100%.

3-Cyclopentyl-3,9-diazaspiro[5.5]undecane 2·TFA 13-{*13*}. ^{1}H NMR (CD_3OD) δ 3.48−3.62 (3H, m), 3.16−3.24 (4H, m), 3.11 (2H, t), 2.13−2.23 (2H, m), 1.79−2.07 (6H, m), 1.65−1.76 (8H, m); EI-MS *m/z* 223 $[M + H]^+$; LC_{area} (ELSD) = 98%.

3-Thiophen-2-ylmethyl-3,9-diazaspiro[5.5]undecane 2·TFA 13{*14*}. ^{1}H NMR (CD_3OD) δ 7.64 (1H, d), 7.34 (1H, d), 7.15 (1H, dd), 4.58 (2H, s), 3.15−3.34 (8H, m), 1.59−2.12 (8H, m); EI-MS *m/z* 251 $[M + H]^+$; LC_{area} (ELSD) = 95%.

3-((*S*)-1-Phenylethyl)-3,9-diazaspiro[5.5]undecane 2·TFA 13{*5*}. ^{1}H NMR (CD_3OD) δ 7.65−7.68 (5H, m), 4.61 (1H, q), 3.79−3.87 (1H, m), 3.47−3.48 (3H, m), 3.25−3.38 (6H, m), 3.04−3.14 (1H, m), 2.08−2.25 (2H, m), 1.76−1.98 (6H, m); EI-MS *m/z* 259 $[M + H]^+$; LC_{area} (ELSD) = 100%.

3-(2-Benzenesulfonylethyl)-3,9-diazaspiro[5.5]undecane 2·TFA 13{*16*}. ^{1}H NMR (CD_3OD) δ 7.98−8.00 (2H, m), 7.79 (1H, tt), 7.68−7.72 (2H, m), 3.75 (2H, t), 3.48 (2H, t), 3.17−3.24 (8H, m), 1.73−1.83 (8H, m); EI-MS *m/z* 323 $[M + H]^+$; LC_{area} (ELSD) = 92%.

3-(1-Benzylpiperidin-4-yl)-3,9-diazaspiro[5.5]undecane 3·TFA 13{*17*}. EI-MS *m/z* 328 $[M + H]^+$; LC_{area} (ELSD) = 99%.

3-(5-Methylisoxazol-3-ylmethyl)-3,9-diazaspiro[5.5]undecane 2·TFA 13{*18*}. ^{1}H NMR (CD_3OD) δ 6.36 (1H, d), 4.43 (2H, s), 3.24−3.40 (8H, m), 2.52 (3H, s), 1.76−1.98 (8H, m); EI-MS *m/z* 250 $[M + H]^+$; LC_{area} (ELSD) = 99%.

4,5α-Epoxy-3-hydroxy-14*β*-hydroxy-6-*β*-(3,9-diazaspiro-[5.5]undec-3-yl)-17-(cyclopropylmethyl)morphinan 3·TFA 13{*20*}: (6.2 mg, 16%), EI-MS *m/z* 480 $[M + H]^+$; LC_{area} (ELSD) = 100%.

2,9-Diazaspirocycles 14. The general microwave cyclization procedure employing resin **22** (62.3 mg, 0.64 mmol g^{-1}, 40.0 μmol), followed by the general resin cleavage procedure [TFA (50% in DCM), 1 mL] yielded the desired 2,9-diazaspirocycle TFA salts **14**{*1*−*20*}.

2-(2-Morpholin-4-yl-ethyl)-2,9-diazaspiro[5.5]undecane 3·TFA 14{*1*}. (16.5 mg, 68%), ^{1}H NMR (CD_3OD) δ 3.96 (4H, t), 3.59−3.72 (4H, m), 3.38−3.44 (4H, m), 3.34−3.36 (4H, m), 3.25 (4H, t), 1.95−2.02 (4H, m), 1.78−1.87 (4H, m); EI-MS *m/z* 305 $[M + H]^+$; LC_{area} (ELSD) = 90%. EI-MS *m/z* 268 $[M + H]^+$; LC_{area} (ELSD) = 100%.

2-(Pyridin-3-yl-methyl)-2,9-diazaspiro[5.5]undecane 2·TFA 14{*2*}. (15.0 mg, 79%), ^{1}H NMR (CD_3OD) δ 8.90 (1H, d), 8.84 (1H, dd), 8.35 (1H, dt), 7.82 (1H, dd), 4.59 (2H, s), 3.24−3.28 (8H, m), 1.79−1.92 (8H, m); EI-MS *m*/*z* 246 $[M + H]^+$; LC_{area} (ELSD) = 89%.

2-(3,4-Dimethoxybenzyl)-2,9-diazaspiro[5.5]undecane 2·TFA 14{*3*}. (15.5 mg, 73%), ^{1}H NMR (CD_3OD) δ 7.11 (1H, d), 7.03−7.04 (2H, m), 4.26 (2H, s), 3.86 (3H, s), 3.85 (3H, s), 3.13−3.25 (8H, m), 1.87−2.04 (4H, m), 1.65−1.81 (4H, m); EI-MS *m*/*z* 305 $[M + H]^+$; LC_{area} (ELSD) = 90%.

2-[2-(4-Chlorophenyl)-ethyl]-2,9-diazaspiro[5.5]undecane 2·TFA 14{*4*}. (15.5 mg, 75%), ^{1}H NMR (CD_3OD) δ 7.39 (2H, dd), 7.32−7.34 (2H, m), 3.35−3.41 (4H, m), 3.18−3.27 (6H, m), 3.70−3.12 (2H, m), 1.77−2.04 (8H, m); EI-MS *m*/*z* 293 $[M + H]^+$; LC_{area} (ELSD) = 92%.

2-(3-Fluorobenzyl)-2,9-diazaspiro[5.5]undecane 2·TFA 14{*5*}. (12.9 mg, 66%), EI-MS *m*/*z* 263 $[M + H]^+$; LC_{area} (ELSD) = 80%.

2-((1*R*,2*R*,5*R*)-6,6-Dimethyl-bicyclo[3.1.1]hept-2-ylmethyl)-2,9-diazaspiro[5.5]undecane 2·TFA 14{*6*}. (13.3 mg, 64%), EI-MS *m*/*z* 291 $[M + H]^+$; LC_{area} (ELSD) = 84%.

2-(2,2-Diphenylethyl)-2,9-diazaspiro[5.5]undecane 2·TFA 14{*7*}. (16.0 mg, 71%), ^{1}H NMR (CD_3OD) δ 7.34−7.43 (8H, m), 7.25−7.29 (2H, m), 4.58 (1H, t), 3.96 (2H, d), 3.16−3.43 (8H, m), 1.67−1.98 (8H, m); EI-MS *m*/*z* 335 $[M + H]^+$; LC_{area} (ELSD) = 92%.

4-[2-(2,9-Diazaspiro[5.5]undec-2-yl)-ethyl]-benzenesulfonamide 2·TFA 14{*8*}. (14.2 mg, 63%), ^{1}H NMR (CD_3OD) δ 7.88 (2H, d), 7.49 (2H, d), 3.30−3.42 (4H, m), 3.15−3.24 (8H, m), 1.73−2.04 (8H, m); EI-MS *m*/*z* 338 $[M + H]^+$; LC_{area} (ELSD) = 90%.

4-(2,9-Diazaspiro[5.5]undec-2-yl)-piperidine-1-carboxylic Acid *tert*-Butyl Ester 2·TFA 14{*9*}. (12.2 mg, 54%), EI-MS *m*/*z* 338 $[M + H]^+$; LC_{area} (ELSD) = 77%.

2-(2-Phenoxyethyl)-2,9-diazaspiro[5.5]undecane 2·TFA 14{*10*}. (14.0 mg, 70%), ^{1}H NMR (CD_3OD) δ 7.29−7.34 (2H, t), 6.99−7.02 (3H, m), 4.38 (2H, t), 3.60−3.64 (2H, m), 3.17−3.38 (8H, m), 1.73−2.04 (8H, m); EI-MS *m*/*z* 275 $[M + H]^+$; LC_{area} (ELSD) = 91%.

2-(5-Methyl-furan-2-ylmethyl)-2,9-diazaspiro[5.5]undecane 2·TFA 14{*11*}. (14.0 mg, 73%), EI-MS *m*/*z* 249 $[M + H]^+$; LC_{area} (ELSD) = 83%.

2-(5-Methyl-3-phenylisoxazol-4-ylmethyl)-2,9-diazaspiro[5.5]undecane 2·TFA 14{*12*}. (14.9 mg, 68%), EI-MS *m*/*z* 326 $[M + H]^+$; LC_{area} (ELSD) = 79%.

2-Cyclopentyl-2,9-diazaspiro[5.5]undecane 2·TFA 14-{*13*}. (13.5 mg, 75%), EI-MS *m*/*z* 223 $[M + H]^+$; LC_{area} (ELSD) = 75%.

2-Thiophen-2-ylmethyl-2,9-diazaspiro[5.5]undecane 2·TFA 14{*14*}. (12.0 mg, 63%), ^{1}H NMR (CD_3OD) δ 7.63 (1H, dd), 7.33 (1H, d), 7.15 (1H, dd), 4.58 (2H, s), 3.16−3.22 (8H, m), 1.73−2.09 (8H, m); EI-MS *m*/*z* 251 $[M + H]^+$; LC_{area} (ELSD) = 82%.

2-((*S*)-1-Phenylethyl)-2,9-diazaspiro[5.5]undecane 2·TFA 14{*15*}. (13.4 mg, 69%), EI-MS *m*/*z* 259 $[M + H]^+$; LC_{area} (ELSD) = 78%.

2-(2-Benzenesulfonylethyl)-2,9-diazaspiro[5.5]undecane 2·TFA 14{*16*}. (11.3 mg, 51%), EI-MS *m*/*z* 323 $[M + H]^+$; LC_{area} (ELSD) = 38%.

2-(1-Benzyl-piperidin-4-yl)-2,9-diazaspiro[5.5]undecane 3·TFA 14{*17*}. (15.4 mg, 58%), EI-MS *m*/*z* 328 $[M + H]^+$; LC_{area} (ELSD) = 79%.

2-(5-Methyl-isoxazol-3-ylmethyl)-2,9-diazaspiro[5.5]-undecane 2·TFA 14{*18*}. (13.8 mg, 72%), ^{1}H NMR (CD_3OD) δ 6.35 (1H, s), 4.41 (2H, s), 3.16−3.35 (8H, m), 2.48 (3H, s), 1.73−2.00 (8H, m); EI-MS *m*/*z* 250 $[M + H]^+$; LC_{area} (ELSD) = 79%.

2-((*S*)-1-Benzyl-2-pyrrolidin-1-yl-ethyl)-2,9-diazaspiro-[5.5]undecane 3·TFA 14{*19*}. (11.4 mg, 42%), EI-MS *m*/*z* 342 $[M + H]^+$; LC_{area} (ELSD) = 68%.

4,5α-Epoxy-3-hydroxy-14*β*-hydroxy-6-*β*-(2,9-diazaspiro-[5.5]undec-2-yl)-17-(cyclopropyl-methyl)morphinan 3·TFA 14{*20*}: EI-MS *m*/*z* 480 $[M + H]^+$; LC_{area} (ELSD) = 70%.

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