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Synthesis of Four Novel Natural Product Inspired Scaffolds for Drug Discovery

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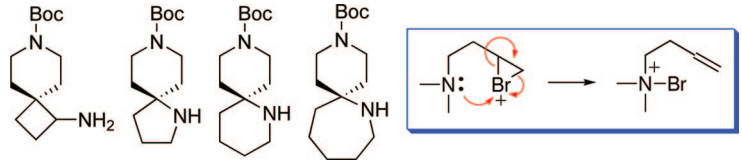

Inspired by the novel spiro structures of a number of bioactive natural products such as the histrionicotoxins, a series of novel spiro scaffolds have been designed and robust syntheses developed. The scaffolds are ready-to-use building blocks and can be easily prepared on a 5−20 g scale. They contain two amino groups (one Boc-protected) and have been designed for ease of conversion to a lead generation library, using either amide formation or reductive amination procedures. The synthesis of the 1,9-diazaspiro[5.5]undecane and 3,7-diazaspiro[5.6]dodecane ring systems was achieved using RCM as the key step. A simple workup procedure is reported for the removal of highly colored ruthenium residues. The synthesis of the 1,8-diazaspiro[4.5]decane scaffold has been achieved using a bromine-mediated 5-endo cyclization of the corresponding 4-aminobutene intermediate under acidic conditions. This is the first example of this type of cyclization to be reported. A novel mechanism involving a bromine transfer reaction from an initially formed bromonium ion to a neighboring nitrogen atom is suggested as the reason for the failure of this type of reaction under "normal" bromination conditions. An unusual rearrangement of a 1-acyl-1,9-diazaspiro[5.5]undecane to the corresponding 9-acyl-1,9-diazaspiro[5.5]undecane is reported.

Introduction

Finding small molecules that selectively modulate protein function remains one of the major challenges in drug discovery. Natural products (NPs), which have been an invaluable source of drug leads for the pharmaceutical industry over many years,[1,2] interact with proteins during their biosynthesis, and there is good reason to believe that this binding to biosynthetic enzymes may correlate with binding to certain drug targets.[3] NPs can therefore be considered as "privileged structures" or biologically validated starting points for the design of compound libraries.[4]

The major hurdle encountered in the development of a newly discovered NP lead is often its structural complexity. The lead compound may have adequate potency and selectivity but poor pharmacokinetics, so the challenge for the medicinal chemist is to turn it into a drug by appropriate modification. In many cases, this is not trivial for reasons of molecular complexity and synthetic accessibility. One possible approach is to use a NP scaffold, a mono- or polycyclic structure having several functional groups available for elaboration.[5] This approach retains some of the features of the original bioactive natural product structure (such as a novel ring system and conformation) but allows the medicinal chemist to introduce more druglike[6,7] functional groups. Moreover, as the natural products database contains many more scaffolds than the drugs database, such

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(1) Lam, K. S. *Trends Microbiol.* **2007**, *15*, 279–289.
(2) Newman, D. J.; Cragg, G. M. *J. Nat. Prod.* **2007**, *70*, 461–477.
(3) McArdle, B. M.; Quinn, R. J. *ChemBioChem* **2007**, *8*, 788–798.
(4) Arve, L.; Voigt, T.; Waldmann, H. *QSAR Comb. Sci.* **2006**, *25*, 449–456.
(5) Khersonsky, S. M.; Chang, Y.-T. *Comb. Chem. High Throughput Screen* **2004**, *7*, 645–652.

10.1021/jo802456w CCC: $40.75
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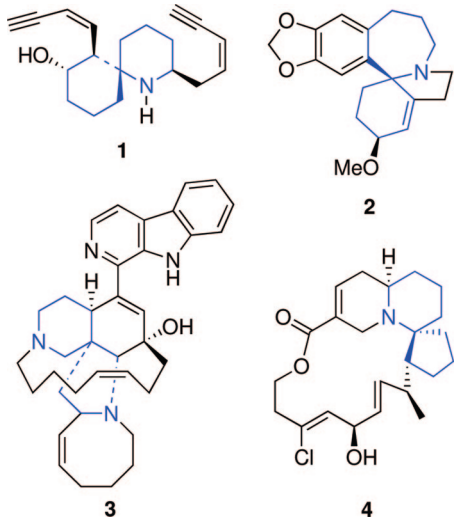
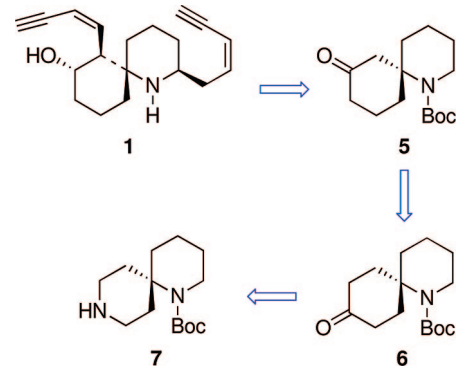


FIGURE 1. Natural products containing spiro rings.

unexplored scaffolds may be promising new starting points in drug discovery.[8] We were interested in scaffolds that were of low molecular weight (<350), "three-dimensional" rather than flat (most commercially available scaffolds are planar molecules), and contained functional groups spread around the molecule. Compounds containing two amino groups (orthogonally protected) were preferred because amide formation and reductive amination are robust reactions that are amenable to automation and library synthesis. We were particularly attracted to the novel spiro scaffolds present in a number of natural products such as histrionicotoxin (**1**),[9] schelhammericine (**2**),[10] manzamine A (**3**),[11] and halichlorine (**4**),[12] which contain the 1-azaspiro[5.5]undecane, 7-azaspiro[5.6]dodecane, 2,7-diazaspiro[4.5]decane, and 6-azaspiro[4.5]decane ring systems, respectively (Figure 1). For example, the histrionicotoxins (such as **1**), which are isolated from the skin of the Colombian poison dart frog, *Dendrobates histrionicus*, are noncompetitive inhibitors of nicotinic acetylcholine receptors and inspired the novel scaffold **7** (the histrionicotoxins are actually not toxic; the family was originally misnamed because of the source; the main toxins in poison dart frogs are pumiliotoxins and batrachotoxin).[13] In arriving at scaffold **7**, we first considered the scaffold **5**, which reflects the main functional groups present in **1** (Scheme 1). For reasons of chemical tractability (**5** could undergo ring-opening via a retro-Michael reaction), we moved the carbonyl to the adjacent 9-position (**6**). In principle, scaffold **6** could be readily converted into a library by reductive amination with a series of secondary amines, followed by removal of the Boc group and acylation with a series of acid chlorides. However,

SCHEME 1. Design of Scaffold 7



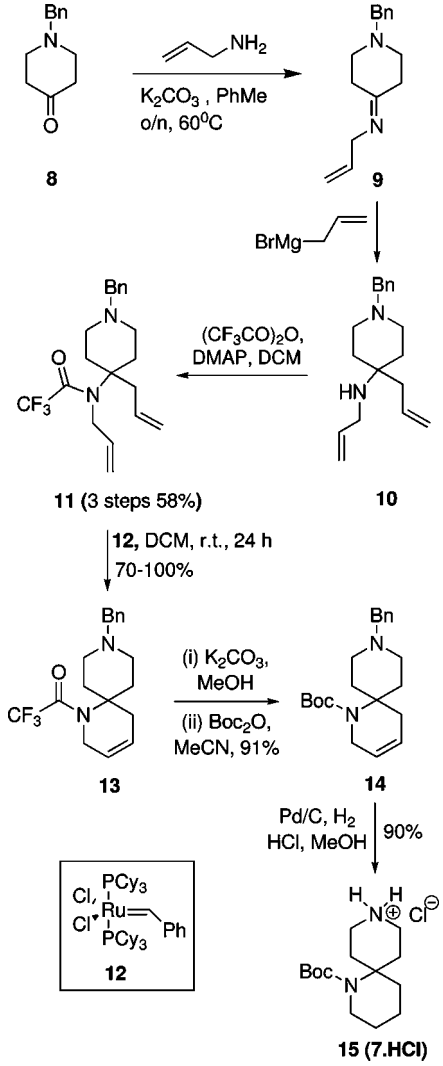
for the reasons noted above, we preferred to target orthogonally protected diamines, so we decided to replace the carbonyl by a nitrogen atom as in scaffold **7**. Scaffold **7** has the added advantage over scaffold **6** that it would not give rise to diastereoisomeric mixtures.

Results and Discussion

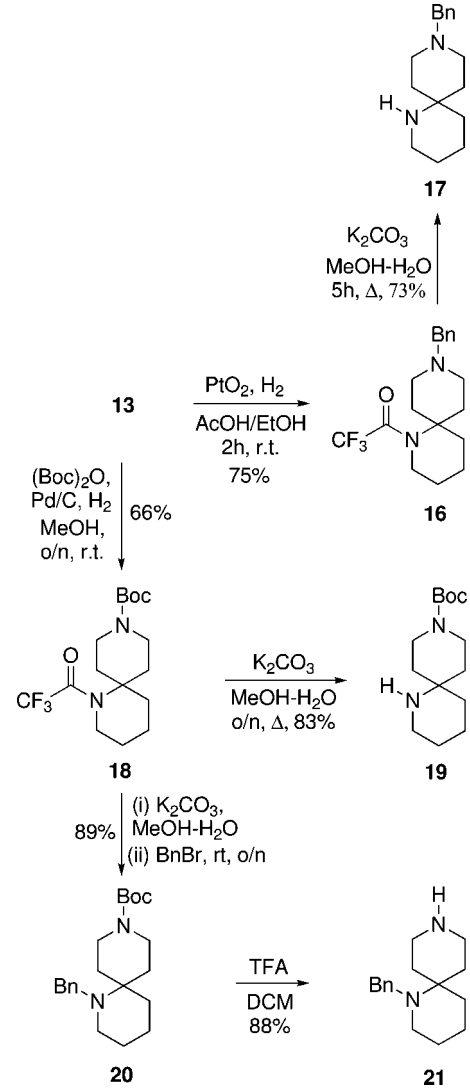
Spiro[5.5] Compounds. In developing a synthesis of the scaffold **7** and related spirocyclic diamino compounds, we required a method that was robust and could be carried out on a 10 g scale with the minimum number of chromatography steps. The starting material was the relatively inexpensive 1-benzyl-4-piperidone (**8**). Treatment of **8** with allylamine (4 equiv) in toluene overnight at 60 °C in the presence of anhydrous potassium carbonate gave the imine **9** (Scheme 2) in high yield (97%). The crude product was then treated with allylmagnesium bromide to give the aminodiene **10** in good yield (82%). An attempted ring-closing metathesis reaction (RCM)[14] on **10** using Grubbs first-generation catalyst (**12**) gave very low yields of the ring-closed product, so the secondary amino group was protected as the trifluoroacetamide **11** (attempted Boc protection of **10** gave only low yields, presumably because of the very hindered nature of the secondary nitrogen adjacent to a tertiary center). The trifluoroacetamide **11** was obtained in good yield (70%) following purification by chromatography on silica gel. Treatment of **11** with **12** (7−9 mol %) in DCM at room temperature under an atmosphere of nitrogen for 24 h followed by filtration through a plug of amino-bonded silica gel to remove the residues of ruthenium gave the spiro compound **13** in quantitative yield. The yields in the RCM reaction varied between 70−100% depending on the mol % of Grubbs catalyst **12** used. With 7 mol % of **12**, the reaction generally didn't go to completion; close to 9 mol % was required for quantitative conversion. It might be possible to reduce the amount of catalyst by employing Grubbs second-generation catalyst,[15] but this catalyst is much more expensive than **12**. To remove the highly colored ruthenium byproduct from the reaction, we first tried the "stirring with DMSO overnight" method.[16] However, we subsequently found that a more efficient procedure was to filter the reaction mixture through a plug of amino-bonded silica. We would recommend this extremely simple and fast procedure for

(6) Walters, W. P.; Murcko, M. A. *Curr. Opin. Chem. Biol.* **1999**, *3*, 384–387.
(7) Leeson, P. D.; Davis, A. M.; Steele, J. *Drug Discovery Today: Technol.* **2004**, *1*, 189–195.
(8) Ortholand, J.-Y.; Ganesan, A. *Curr. Opin. Chem. Biol.* **2004**, *8*, 271–280.
(9) For a review, see: Sinclair, A.; Stockman, R. A. *Nat. Prod. Rep.* **2007**, *24*, 298–326.
(10) Johns, S. R.; Lamberton, J. A.; Sioumis, A. A. *Aust. J. Chem.* **1969**, *22*, 2219–31.
(11) (a) Nishida, A.; Nagata, T.; Nakagawa, M. *Top. Heterocycl. Chem.* **2006**, *5*, 255–280. (b) Magnier, E.; Langlois, Y. *Tetrahedron* **1998**, *54*, 6201–6258.
(12) (a) Kuramoto, M.; Tong, C.; Yamada, K.; Chiba, T.; Hayashi, Y.; Uemura, D. *Tetrahedron Lett.* **1996**, *37*, 3867–3870. (b) Arimoto, H.; Hayakawa, I.; Kuramoto, M.; Uemura, D. *Tetrahedron Lett.* **1998**, *39*, 861–862.
(13) Daly, J. W.; Spande, T. F.; Garraffo, H. M. *J. Nat. Prod.* **2005**, *68*, 1556–1575.
(14) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18–29.
(15) Wright, D. L.; Schulte, J. P., II; Page, M. A. *Org. Lett.* **2000**, *2*, 1847–1850.
(16) Ahn, Y. M.; Yang, K.; Georg, G. I. *Org. Lett.* **2001**, *3*, 1411–1413.

SCHEME 2. Synthesis of Scaffold 7



SCHEME 3. Synthesis of Scaffolds 17, 19, and 21

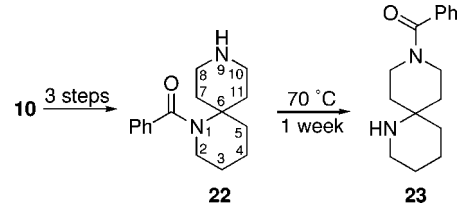


the clean up of RCM reactions involving basic substrates (we have not tried it with nonbasic substrates).[17]

The trifluoroacetyl protecting group was removed by refluxing in methanol with potassium carbonate for 3 h, followed by installation of the Boc group and purification by chromatography on silica gel to give **14** in high yield (91%). Presumably, the secondary nitrogen is less hindered in the spiro compound (where the two allyl groups have been shortened and "tied back") than in compound **10**, but reaction with Boc anhydride was still sluggish and took 3 days at room temperature.

The final step was a combined hydrogenation/hydrogenolysis in the presence of 1 equiv of HCl in methanol to give the desired scaffold **7** as its white crystalline hydrochloride salt **15** in high yield (90%). In summary, the scaffold **7** was synthesized in six steps in an overall yield of 47%. Each of the steps is robust and can be carried out easily in the laboratory on a 10−20 g scale. Only two chromatography steps are required. The intermediate **13** can be obtained in four steps and 58% overall yield and can be easily converted into the complementary scaffolds **17**, **19**, and **21** (Scheme 3). None of these compounds has been described previously (the intermediate **18** has been prepared from the more expensive 1-Boc-4-piperidone, but scant experimental details were provided).[18]

SCHEME 4. Synthesis of Scaffolds 22 and 23



Two other closely related scaffolds prepared were the benzamides **22** and **23**. Benzamide **22** was prepared on a 20 g scale in three steps from the intermediate **10** (Scheme 4) using a procedure analogous to that in Scheme 2 (five steps from *N*-benzylpiperidone **8**, overall yield 49%). During the synthesis of **22**, it was observed that a small amount of the isomeric benzamide **23** was formed on standing in methanol. Upon further investigation, it was found that **22**, a viscous oil, rearranged to **23** even in the absence of solvent (after 1 week at 70 °C, virtually none of the more polar **22** remained). In methanol,

(17) See also: McEleney, K.; Allen, D. P.; Holiday, A. E.; Crudden, C. M. *Org. Lett.* **2006**, *8*, 2663–2666.

(18) Gracias, V.; Gasiecki, A. F.; More, J. D.; Akritopoulou-Zanze, I.; Djuric, S. W. *Tetrahedron Lett.* **2006**, *47*, 8977–8980.

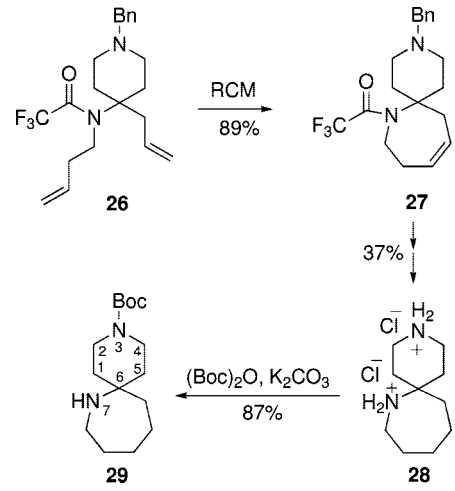
the reaction appears to be bimolecular rather than unimolecular, as it is concentration-dependent. Presumably, the mechanism of this unusual and unexpected rearrangement involves attack by the free NH group of one molecule on the amide carbonyl of another, although it is conceivable that the process is intramolecular in the absence of solvent—a study of molecular models suggests that if the "upper" piperidine ring adopts a boat conformation, and the amide nitrogen is axial, the free NH is in very close proximity to the amide carbonyl. We believe that the unusual lability of the acyl group on the 1-nitrogen is a result of steric assistance.[19] Normally, the amide group would be expected to be flat, but in these spiro compounds, the benzoyl group is subject to steric compression by hydrogens on the adjacent ring (the hydrogens on C-8 or C-10 if the nitrogen is axial, and the hydrogens on C-7 or C-11 if equatorial). We suggest that this causes the bond between the carbonyl and the nitrogen atom to twist out of the plane, thereby reducing the resonance interaction between the nitrogen lone pair and the carbonyl, and thus activating the carbonyl toward nucleophilic attack. This suggestion is supported by the infrared stretching frequency of the carbonyl group in **22** ($\nu = 1636$ cm^{-1} for the HCl salt, **24**), which is considerably higher than that in the isomeric benzamide **23** ($\nu = 1611$ cm^{-1} for the HCl salt, **25**).

It is important to be aware of the potential lability of acyl groups on the 1-nitrogen of these scaffolds when preparing an amide library from scaffolds **17** or **19**, for example. Once the protecting group (Boc or benzyl respectively) is removed, a free NH group is generated and there is the potential for acyl migration (as in **22** to **23**) on standing or on heating. We have found that this migration does not occur if the free amine is converted to its hydrochloride salt. Thus, the hydrochloride salts of **22** (**24**) and **23** (**25**) are stable compounds and can be stored for more than a year without change.

Spiro[5.6] Compounds. The spirocyclic diamino scaffold **29** was inspired by the spiro system present in the cephalotaxus alkaloid schelhammericine[10] (**2**). Our approach to this scaffold was the same as that outlined in Scheme 2 for the synthesis of the spiro[5.5] intermediate **13**: addition of 3-butenylmagnesium bromide to the imine **9**, followed by protection of the nitrogen and RCM, should give the corresponding spiro[5.6] intermediate. Unfortunately, the 3-butenyl Grignard reagent did not undergo addition to the imine, a result consistent with the findings of others.[18] The imine **9** presumably undergoes proton abstraction by the Grignard rather than addition, as the only product isolated after workup is the *N*-benzylpiperidone **8**. Since allylmagnesium bromide adds readily to these imines, we were able to prepare the desired scaffold **29** by interchanging the allyl and butenyl groups, i.e., by first preparing the imine from 3-butenylamine and then addition of allylmagnesium bromide. Protection of the amino group as its trifluoroacetate gave the intermediate **26** (68% yield from **8** after purification by chromatography).

Treatment of **26** with Grubbs catalyst **12** gave the spiro[5.6] intermediate **27** in high yield (89%). It was found that the RCM reaction to form the 7-membered ring (Scheme 5) was not as efficient as that to form the 6-membered spiro compound **13**. To effect complete conversion of **26** to **27** required 15 mol % of catalyst (added in two portions) and stirring in DCM for 3 days. The intermediate **27** was then converted into the desired 3-Boc-3,7-diazaspiro[5.6] scaffold **29** by standard protection/deprotection procedures. As in the case of scaffold **7**, we required a synthesis of **29** that would produce sufficient material for preparation of a small library. We were able to achieve this with only two chromatography steps, but the overall (unoptimised) yield was rather low (5%, seven steps from *N*-benzyl-4-piperidone).

SCHEME 5. Synthesis of Scaffold 29



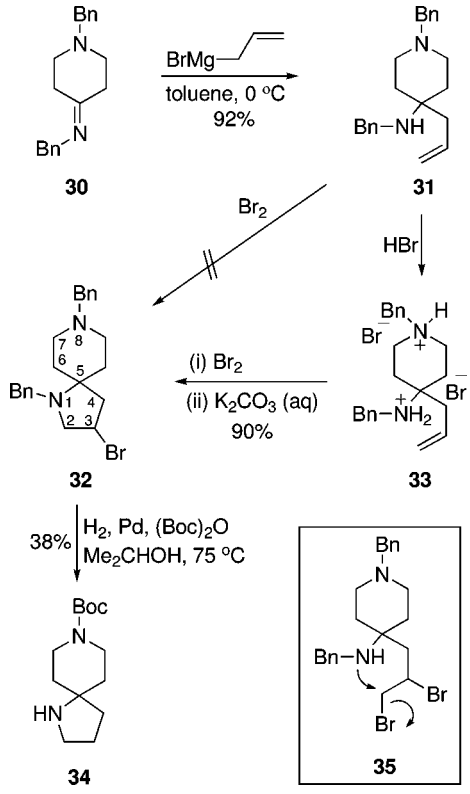
Spiro[4.5] Compounds. The spirocyclic scaffold **34** was inspired by the spiro system present in halichlorine (**4**)[12] and manzamine A (**3**),[11] the latter containing a diazaspiro system within its complex polycyclic skeleton. However, the synthesis of the spiro[4.5] scaffold **34** presented more of a challenge. As was found with the butenyl Grignard reagent, treatment of the imine **9** with vinylmagnesium bromide resulted only in the isolation of *N*-benzylpiperidone **8**. With no simple way of converting the piperidone **5** into an imine bearing a vinyl group on the nitrogen, it was not possible to employ the RCM strategy used for the synthesis of **7** or **29**. As the allyl Grignard addition to an imine chemistry worked so well and could be scaled up to at least 50 g, we considered a bromine-mediated cyclization of the 4-aminobutene intermediate **31** (prepared in 89% yield from *N*-benzylpiperidone **8** and benzylamine using the same conditions as those used for the preparation of intermediate **10**). However, treatment of **31** with bromine in DCM failed to give the cyclized product **32** (Scheme 6). We also investigated *N*-bromosuccinimide, iodine, *N*-iodosuccinimide, phenylselenium chloride, and phenylselenium bromide as alternative electrophilic reagents. Only phenylselenium bromide resulted in a cyclized product, but the yield was low (18%) and this reaction was not investigated further.

We thought that in the case of attempted bromine-mediated cyclization, **31** might be undergoing preferential bromination on nitrogen, thereby preventing a cyclization reaction. It was decided, therefore, to carry out the bromination on the HBr salt of **31**. This strategy was successful. Thus, **31** was treated with HBr (2.5 equiv) in methanol (generated by addition of acetyl bromide to methanol) and evaporated to give a foam. DCM /methanol (10:1) was added and the mixture cooled to −78 °C, followed by the addition of bromine (1.5 equiv). The mixture was stirred at 0 °C for 3 h, potassium carbonate and water were added, and stirring was continued for a further 16 h at rt. The bromo spiro[4.5] product **32** was isolated from the DCM layer in excellent yield (90%) after purification by chromatography.

Conversion of **32** to the required scaffold **34** required reduction of the bromo group, removal of the two benzyl

(19) ElielE. L. WilenS. H. ManderL. N. *Stereochemistry of Organic Compounds*; John Wiley & Sons: New York, 1994; p 721.

SCHEME 6. Synthesis of Scaffold 34

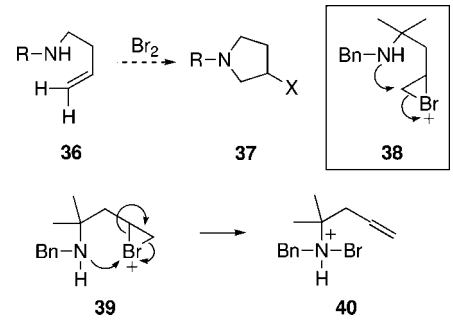


protecting groups, and introduction of the Boc group on the 8-nitrogen. This was achieved in a one-pot procedure by hydrogenolysis in the presence of Boc anhydride at 75 °C for 2 days (the higher temperature was necessary for the reduction of the bromo compound) to give **34** (38%). We attribute the rather poor yield to partial loss of the Boc group either during the reaction or during workup and possibly also the formation of some di-Boc product (both the free diamine and the di-Boc products would be removed during the reaction workup). We did not optimize this reaction.

The cyclization reaction (**31** to **32**) almost certainly proceeds via bromine addition to the olefin to give the dibromide **35**, followed by a *5-exo-tet* cyclization.[20] In support of this, the mass spectrum (electrospray, +ve ion) of the reaction mixture after the addition of bromine but before the addition of the potassium carbonate, showed peaks at 479, 481, and 483, corresponding to the protonated dibromide **35**, whereas after stirring overnight with potassium carbonate, these peaks had disappeared, being replaced by peaks at 399 and 401, corresponding to the protonated monobromo derivative **32**.

Interestingly, there are no known examples of bromonium ion-mediated cyclizations of the type **36** to **37** (Scheme 7) where R = alkyl or hydrogen,[21] and the direct cyclization of amines to heterocycles containing nitrogen has rarely been employed

SCHEME 7. Cyclization Mediated by Bromonium Ions



owing to the difficulties connected with this kind of reaction.[22] We suggest that the main reason for the failure of this type of reaction is competitive bromination on nitrogen (to give an unstable N-bromo derivative),[23] possibly because the *5-endo-tet* process **38** is disfavored by Baldwin's rules.[24] Although the formation of a *N*-bromo derivative could occur directly, we believe it is more likely to occur via a bromine transfer reaction from an initially formed bromonium ion **39** (to give **40**). In support of this proposed mechanism, a key step in the recent synthesis of (−)-epibatidine was the bromination of a 4-aminocyclohexene. The dibromide could only be obtained when the bromination was carried out in the presence of a large (10-fold) excess of $Et_4N^+Br^-$.[25] In the present work, the bromination was carried out in the presence of HBr. This achieves the same purpose as addition of $Et_4N^+Br^-$; it increases the concentration of bromide ion (which favors interception of the bromonium ion **39**, to give the dibromide **35**), but also, by protonating the nitrogen atom, formation of an *N*-bromo compound is prevented.

In summary, the simple expedient of carrying out the bromination on the protonated amino alkene, as illustrated here, has enabled the synthesis of a pyrolidine ring system from a 4-aminobutene. This methodology may be more generally applicable to the synthesis of heterocycles containing nitrogen and complements the iodine-mediated cyclization of but-1-enylamines.[26,27]

Spiro[3.5] Compounds. Synthesis of the spiro[3.5] scaffold **41** containing a 4-membered (azetidine) ring was a logical extension to the series of scaffolds **29**, **7**, and **34** (containing 7-, 6-, and 5-membered rings, respectively). However, the core structure of this 1,7-diazaspiro[3.5] system (i.e., **41** without the Boc protecting group) is well-known in the patent literature,[28] so we turned our attention instead to the novel scaffold **43**. Surprisingly, although the ketone **42** has been prepared, scaffold **43** has not been reported. Ketone **42** is readily prepared on a large (20 g) scale in four steps from 1-Boc-4-piperidone using literature procedures.[29] Reductive amination of **42** with benzylamine and sodium triacetoxyborohydride followed by hy-

(20) There are a number of examples of cyclization of 4-bromoamines; see, for example: (a) Minin, P. L.; Walton, J. C. *J. Org. Chem.* **2003**, *68*, 2960–2963. (b) Booth, H.; King, F. E.; Mason, K. G.; Parrick, J.; Whitehead, R. L. St. D. *J. Chem. Soc.* **1959**, 1050–4. (c) Drake, N. L.; Ross, A. B. *J. Org. Chem.* **1958**, *23*, 794–6. (d) Prelog, V.; Szpilfogel, S. *Helv. Chim. Acta* **1945**, *28*, 178–82.

(21) Cyclization is possible when R = acyl; see, for example: (a) Movassaghi, M.; Schimidt, M. A.; Ashenhurst, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1485–1487. (b) Gomez-Sanchez, E.; Soriano, E.; Marco-Contelles, J. *J. Org. Chem.* **2007**, *72*, 8656–8670. (c) Kapferer, P.; Vasella, A. *Helv. Chim. Acta* **2004**, *87*, 2764–2789. (d) Corey, E. J.; Loh, T. P.; AchyuthaRao, S.; Daley, D. C.; Sarshar, S. *J. Org. Chem.* **1993**, *58*, 5600–2.

(22) Cardillo, G.; Orena, M. *Tetrahedron* **1990**, *46*, 3321–3408.

(23) There is recent literature precedent for this in the conversion of quinotoxine into *N*-bromoquinotoxine: Smith, A. C.; Williams, R. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 1736–1740.

(24) Smith, M. B.; March, J. *March's Advanced Organic Chemistry*; 6th ed.; John Wiley & Sons: Hoboken, NJ, 2007; p *306*.

(25) Lee, C.-L. K.; Loh, T.-P. *Org. Lett.* **2005**, *7*, 2965–2967.

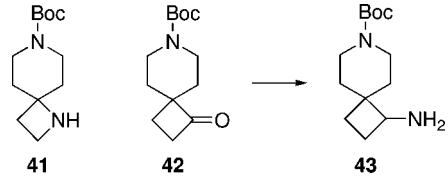
(26) Diaba, F.; Puigbó, G.; Bonjoch, J. *Eur. J. Org. Chem.* **2007**, *303*, 8–3044.

(27) Chang, K.-T.; Jang, K. C.; Park, H.-Y.; Kim, Y.-K.; Park, K. H.; Lee, W. S. *Heterocycles* **2001**, *55*, 1173–1179.

(28) See, for example: Adam, G.; Cesura, A.; Jenck, F.; Kolczewski, S.; Roever, S.; Wichmann, J. Eur. Pat. Appl. EP 970957, 2000.

(29) (a) Trost, B. M.; Bogdanowicz, M. J. *J. Am. Chem. Soc.* **1973**, *95*, 5298–5307. (b) Finke, P. E.; Loebach, J. L.; Parker, K. A.; Plummer, C. W.; Mills, S. G. U.S. Pat. Appl. US 2005070609, 2005.

SCHEME 8. Spiro[3.5] Scaffolds



41 42 43

drogenolysis gave the desired scaffold **43** in good yield (84%) on a 5−10 g scale. The (racemic) product was purified by conversion to its hydrochloride salt and recrystallization. We did not attempt to resolve **43** into its enantiomers as we considered that the racemic compound was adequate for the preparation of a lead generation library.

In summary, inspired by the novel spiro structures of a number of bioactive natural products, we have developed methods for the synthesis of four new scaffolds for drug discovery. Related spirocyclic scaffolds have had a relatively high success rate in the discovery of chemical entities interfering with biological systems, especially in the GPCR area.[30] The spiro[4.5], [5.5], and [5.6] systems described here give the scaffolds a 3-D shape that reflects the original natural product architecture. The scaffolds contain two amino groups (one Boc-protected) and have been designed for ease of conversion to a lead generation library, using either amide formation or reductive amination procedures. The scaffolds are ready-to-use building blocks and can be easily prepared on a 5−20 g scale. Some interesting new chemistry has come out of this work. The first was the discovery of an unusual rearrangement of a 1-acyl-1,9-diazaspiro[5.5]undecane to the corresponding 9-acyl-1,9-diazaspiro[5.5]undecane. The second was the development of a simple methodology for effecting the bromine-mediated 5-endo cyclization of 4-aminobutenes, a reaction that has not previously been reported. A novel mechanism involving a bromine transfer reaction from an initially formed bromonium ion to a neighboring nitrogen atom is suggested as the reason for the failure of this type of reaction under "normal" bromination conditions.

Experimental Section

1-Benzyl-4-allyl-4-(*N*-allyl-*N*-trifluoroacetylamino)piperidine (11). 1-Benzyl-4-piperidone **8** (16 g, 84 mmol) and anhydrous K_2CO_3 (24.3 g, 17.6 mmol) were stirred in toluene (160 mL) under N_2. Allylamine (26 mL, 347 mmol, 4 equiv) was added at room temperature. The mixture was stirred overnight at 60 °C, filtered, and evaporated to dryness to give the imine **9** (18.78 g, 97%). ^{1}H NMR (500 MHz, C_6D_6): δ 1.99−2.01 (t, J = 6.0 Hz, 2H), 2.17−2.20 (t, J = 5.7 Hz, 2H), 2.34−2.36 (t, J = 5.7 Hz, 2H), 2.41−2.44 (t, J = 6.0 Hz, 2H), 3.24 (s, 2H), 3.84−3.85 (d, J = 5.5 Hz, 2H), 5.05−5.07 (dd, J = 10.0 Hz, J = 1.5 Hz, 1H), 5.22−5.26 (dd, J = 2.0 Hz, J = 17.0 Hz, 1H), 5.99−6.06 (m, 1H), 7.10−7.20 (m, 5H). Imine **9** was not purified but used directly in the next step. To the imine **9** (18.78 g) dissolved in toluene (80 mL) was added allylmagnesium bromide (100 mL, 1 mol/L in ether) at 0 °C under N_2. The mixture was stirred overnight at room temperature. Water (750 mL) was added to the mixture. The organic layer was separated, evaporated to dryness, and set aside. The aqueous layer was filtered and extracted with DCM (4 × 250 mL). The organic layers were combined, and the solvent was concentrated to a volume of 200 mL. The resulting solution was washed with water (100 mL), dried over $MgSO_4$, and evaporated to dryness to give the diallyl derivative **10** (18.92 g, 82%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.60−1.62 (m, 4H), 2.21 (d, J = 8.0 Hz, 2H), 2.43−2.54 (m, 4H), 3.16 (d, J = 5.5 Hz, 2H), 3.54 (s, 2H), 5.08−5.15 (m, 3H), 5.22−5.25 (m, 1H), 5.80−5.89 (m, 1H), 5.94−6.01 (m, 1H), 7.25−7.39 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 35.2 (C3/5), 42.0 (4-allyl), 44.0 (*N*-allyl), 49.5 (C2/6), 52.4 (C4), 63.4 (benzyl), 115.3 (4-allyl), 118.2 (*N*-allyl), 127.0, 128.3, 129.2 (benzyl), 134.1 (4-allyl), 138.0 (*N*-allyl), 139.0 (benzyl). LRMS (ESI): calcd for ($M + H^+$) $C_{18}H_{26}N_2$ 271, found 271. The diallyl derivative **10** was not purified but used directly in the next step. To **10** (18.9 g, 70 mmol) were added DMAP (862 mg, 7.0 mmol) and DCM (90 mL) under N_2. TFA anhydride (15 mL, 108 mmol) was added at 0 °C. The mixture was stirred overnight at room temperature. DCM (300 mL) was added. The mixture was washed with saturated $NaHCO_3$ solution (200 mL) and water (250 mL) and dried over $MgSO_4$. The solvent was evaporated and the product purified by flash chromatography (DCM, 2% MeOH, 0.1% NEt_3) to give 1-benzyl-4-allyl-4-(*N*-allyl-*N*-trifluoroacetylamino)piperidine (**11**, 17.9 g, 70%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.10−2.14 (m, 2H), 2.31−2.37 (m, 4H), 2.69−2.71 (m, 2H), 2.85−2.86 (d, J = 7.0 Hz, 2H), 3.52 (s, 2H), 4.03−4.04 (m, 2H), 5.08−5.14 (m, 2H), 5.20−5.24 (m, 2H), 5.64−5.73 (m, 1H), 5.82−5.88 (m, 1H), 7.27−7.36 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 33.70 (C3/5), 35.3 (4-allyl), 47.1 (*N*-allyl), 50.2 (C2/6), 63.1 (benzyl), 64.6 (C4), 116.7 (q, J = 288 Hz, CF_3), 117.1 (4-allyl), 119.4 (*N*-allyl), 127.4, 128.6. 129.4 (benzyl), 133.0 (4-allyl), 136.5 (*N*-allyl), 138.3 (benzyl), 158.1 (q, J = 34 Hz, CO). LRMS (ESI): calcd for ($M + H^+$) $C_{20}H_{25}F_3N_2O$ 367, found 367.

***tert*-Butyl 1,9-Diazaspiro[5.5]undecane-1-carboxylate Hydrochloride (15).** A solution of the diene **11** (10.0 g, 27.3 mmol) in dichloromethane (220 mL) was evacuated and filled three times with nitrogen before addition of Grubbs catalyst (1st generation, 2.00 g, 2.43 mmol). The reaction mixture was stirred under an atmosphere of nitrogen for 24 h. The reaction mixture was then filtered through a plug of amino-bonded silica, and the residues were washed with DCM (3 × 100 mL). The solvent was removed from the filtrate in vacuo to give the spiro compound **13** (9.23 g, ∼100%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.75−1.80 (m, 2H), 2.12−2.30 (m, 4H), 2.65−2.71 (m, 4H), 3.54 (s, 2H), 4.00 (bs, 2H), 5.68−5.70 (m, 1H), 5.79−5.81 (m, 1H), 7.27−7.36 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 33.8 (C7/11), 35.3 (C5), 43.0 (C2), 49.9 (C8/10), 58.3 (C6), 63.0 (benzyl), 116.4 (q, J = 289 Hz, CF_3), 123.5 (C2), 126.0 (C3), 127.5, 128.5, 129.5 (benzyl), 137.7 (benzyl), 158.8 (q, J = 34 Hz, CO). LRMS (ESI): calcd for ($M + H^+$) $C_{18}H_{21}F_3N_2O$ 339, found 339. The spiro intermediate **13** was not purified but used directly in the next step. A solution of **13** (8.19 g, 24.20 mmol) and potassium carbonate (6.69 g, 48.41 mmol) in MeOH (160 mL) was heated at reflux for 3 h. The reaction mixture was cooled and the solvent removed in vacuo. Water (200 mL) was added to the residue and the mixture extracted with chloroform (3 × 100 mL). The organic phase was dried ($MgSO_4$) and filtered and the solvent removed in vacuo. The crude residue was then dissolved in acetonitrile (160 mL), di-*tert*-dibutyl carbonate (10.56 g, 48.40 mmol) added, and the reaction mixture stirred for 3 d. The solvent was then removed in vacuo, saturated sodium hydrogen carbonate (100 mL) added, and the mixture extracted with

(30) (a) See, for example: Tang, F.-Y.; Qu, L.-Q.; Xu, Y.; Ma, R.-J.; Chen, S.-H. *Synth. Commun.* **2007**, *37*, 3793–3799. (b) Gasiecki, A. F.; Cross, J. L.; Henry, R. F.; Gracias, V.; Djuric, S. W. *Tetrahedron Lett.* **2008**, *49*, 6286–6288. (c) Ihle, D. C.; Li, G.; Wustrow, D. J.; Hodgetts, K. PCT Int. Appl. WO 2008024692, 2008, 68 pp. (d) Schudok, M.; Wagner, M.; Bauer, A.; Kohlmann, A. PCT Int. Appl. WO 2007137738, 2007, 153 pp. (e) Kusumi, K.; Kokubo, M.; Ochiai, H.; Shibayama, S. PCT Int. Appl. WO 2007132846, 2007, 178 pp. (f) Berk, S. C.; Close, J.; Hamblett, C.; Heidebrecht, R. W.; Kattar, S. D.; Kliman, L. T.; Mampreian, D. M.; Methot, J. L.; Miller, T.; Sloman, D. L.; Stanton, M. G.; Tempest, P.; Zabierek, A. A. U.S. Pat. Appl. US 2007117824, 2007, 96 pp. (g) Boerjesson, L.; Connolly, S.; Johansson, H.; Kristoffersson, A.; Linnanen, T.; Shamovsky, I.; Skrinjar, M. PCT Int. Appl. WO 2007030061, 2007, 257 pp. (h) Eriksen, B. L.; Peters, D.; Nielsen, E. O.; Redrobe, J. P. PCT Int. Appl. WO 2007000463, 2007, 27 pp. (i) Torisu, K.; Nakai, Y.; Egashira, H.; Sakai, M. PCT Int. Appl. WO 2006006490, 2006, 161 pp. (j) Janssens, F. E.; Schoentjes, B.; Coupa, S.; Poncelet, A. P.; Simonnet, Y. R. F. PCT Int. Appl. WO 2005097795, 2005, 107 pp. (k) Tsuchiya, Y.; Nomoto, T.; Osawa, K.; Kawakami, K.; Owaki, K.; Nishikibe, M. Jpn. Pat. JP 2001039950, 2001, 36 pp.

chloroform (3 × 100 mL). The organic phase was dried ($MgSO_4$) and filtered and the solvent removed in vacuo to give a residue that was purified by flash chromatography using ethyl acetate/hexane (3/7) to give the alkene **14** (7.55 g, 91%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.47 (s, 9H), 1.71−1.75 (m, 2H), 2.16 (m, 2H), 2.41 (t, J = 10 Hz, 2H), 2.56−2.58 (m, 2H), 2.69 (*s*, 2H), 3.60 (s, 2H), 3.99 (s, 2H), 5.63−5.65 (m, 1H), 5.70−5.72 (m, 1H), 7.25−7.40 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 28.8 (Boc), 34.8 (C7/11), 35.7 (C5), 44.0 (C2), 50.2 (C8/10), 55.1 (C6), 63.1 (benzyl), 80.0 (C−O), 124.9 (C3), 125.5 (C4), 127.7, 128.6, 129.8 (benzyl), 156.1 (CO). LRMS (ESI): calcd for (M + H$^+$) $C_{21}H_{30}N_2O_2$ 343, found 343. The alkene **14** was converted directly into the desired scaffold **15** by careful addition of 1.0 equiv of HCl followed by reduction/hydrogenolysis: Acetyl chloride (1.82 mL, 25.55 mmol) was dissolved in methanol (150 mL). The resulting solution of HCl in methanol was added to a solution of alkene **14** (8.75 g, 25.55 mmol) in methanol (725 mL), and to this solution was added 10% palladium on carbon (6.15 g). The mixture was evacuated and flushed three times with hydrogen and allowd to stir under an atmosphere of hydrogen for 18 h. The reaction mixture was then filtered through Celite, and the residues were washed with methanol (3 × 200 mL). The methanol was reduced to a minimum in vacuo and toluene added. The solvent was again reduced to a minimum in vacuo causing the product to precipitate. The product was collected by filtration with washing with toluene and ether and drying to give *tert*-butyl 1,9-diazaspiro[5.5]undecane-1-carboxylate hydrochloride (**15**, 6.67 g, 90%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.45 (s, 9H, Boc), 1.49 (m, 2H), 1.61 (m, 2H), 1.68 (m, 2H), 1.77 (app t, J = 12.5 Hz, 2H), 2.96 (app d, J = 14.5 Hz, 2H), 3.16, (m, 2H), 3.32 (app d, J 12.5 Hz, 2H), 3.43 (app t, J 5.5 Hz, 2H, H2), 9.40 (br s, 2H, NH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ 19.5 (C4), 25.0 (C3), 28.7 (Boc), 32.5 (C5), 35.7 (C7/11), 40.8 (C8/10), 42.7 (C2), 56.0 (C6), 80.4 (C−O), 155.9 (CO). HRMS (ESI): calcd for (M + H$^+$) $C_{14}H_{26}N_2O_2$ 255.2067, found 255.2075.

9-Benzyl-1,9-diazaspiro[5.5]undecane (17). The spiro intermediate **13** (3.85 g, 11.4 mmol) was dissolved in EtOH/AcOH (9:1, 110 mL) under N_2. The catalyst PtO_2 (232 mg, 1.1 mmol, 10%) was added. The flask was evacuated and flushed with N_2 followed by H_2. The mixture was stirred 2 h at room temperature under an atmosphere of hydrogen (balloon) and evaporated to dryness. After dilution with CH_2Cl_2 (200 mL), the crude product was washed with saturated $NaHCO_3$ solution (200 mL) and water (200 mL). The organic layer was dried ($MgSO_4$) and evaporated to dryness. The crude product was purified by flash chromatography (DCM, 1% MeOH) to give compound **16** (2.9 g, 75%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.57−1.63 (m, 2H), 1.67 (m, 4H), 1.77−1.78 (m, 2H), 2.43−2.47 (m, 4H), 2.87−2.92 (m, 2H), 3.48−3.51 (m, 4H), 7.24−7.35 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.3 (C4), 24.9 (C3), 31.9 (C5), 32.3 (C7/11), 41.5 (C2), 50.0 (C8/10), 61.0 (C6), 62.8 (C−O), 116.9 (q, J = 287 Hz, CF_3), 127.2, 128.4, 129.3, 138.6 (benzyl), 157.1 (q, J = 34 Hz, CO). LRMS (ESI): calcd for (M + H$^+$) $C_{18}H_{23}F_3N_2O$ 341, found 341. Compound **16** (835 mg, 2.46 mmol) was dissolved in MeOH/H_2O (1:1, 20 mL), and K_2CO_3 (1.64 g, 11.9 mmol, 5 equiv) was added. The mixture was stirred for 5 h at 90 °C. The crude product was evaporated to dryness and then purified by chromatography on basic alumina (DCM then DCM, 2% MeOH) to give 9-benzyl-1,9-diazaspiro[5.5]undecane (**17**, 440 mg, 73%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.41−1.43 (m, 2H), 1.48−1.50 (m, 2H), 1.52−1.55 (m, 2H), 1.60−1.63 (m, 4H), 2.34−2.39 (m, 2H), 2.42−2.46 (m, 2H), 2.76−2.79 (m, 2H), 3.50 (s, 2H), 7.22−7.32 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.3 (C4), 27.1 (C3), 35.7 (C7/11), 36.6 (C5), 40.7 (C2), 49.3 (C6), 49.5 (C8/10), 63.5, 127.2, 128.4, 129.4, 138.7 (benzyl). HRMS (ESI): calcd for (M + H$^+$) $C_{16}H_{24}N_2$ 245.2012, found 245.2001.

***tert*-Butyl 1,9-Diazaspiro[5.5]undecane-9-carboxylate (19).** The spiro intermediate **13** (2.75 g, 8.14 mmol) was dissolved in MeOH (64 mL) under N_2. $(Boc)_2O$ (5.62 g, 25.7 mmol, 3 equiv) was added. The flask was evacuated and flushed with N_2. The catalyst Pd/C (1.31 g, 1.2 mmol, 10%) was added. The flask was evacuated and flushed with N_2 followed by H_2. The mixture was stirred overnight at room temperature under an atmosphere of hydrogen (balloon). The reaction mixture was filtered through Celite, evaporated to dryness, and purified by flash chromatography (DCM, 1% MeOH) to give compound **18** as a white solid (2.2 g, 77%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.45 (s, 9H), 1.49−1.53 (m, 2H), 1.69−1.73 (m, 4H), 1.80−1.82 (m, 2H), 2.80−2.85 (m, 2H), 3.27−3.32 (m, 2H), 3.50−3.57 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 16.9 (C4), 24.2 (C3), 28.6 (Boc), 31.5 (C5), 32.0 (C7/11), 40.4 (C8/10), 41.5 (C2), 60.7 (C6), 79.8 (C−O), 116.8 (q, J = 288 Hz, CF_3), 155.0 (CO), 157.2 (q, J = 34 Hz, CO). LRMS (ESI): calcd for (M + Na$^+$) $C_{16}H_{25}F_3N_2O_3$ 373, found 373. Compound **18** (624 mg, 1.78 mmol) was dissolved in MeOH/H_2O (1:1, 18 mL) and K_2CO_3 (1.24 g, 9.0 mmol, 5 equiv) added. The mixture was stirred for 2.5 h at 90 °C, evaporated to dryness, and purified by chromatography on neutral alumina (DCM, Pent 90:10, then DCM, and DCM 2% MeOH) to give *tert*-butyl 1,9-diazaspiro[5,5]undecane-9-carboxylate (**19**) (332 mg, 83%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.35−1.52 (m, 19H), 2.72−2.74 (m, 2H), 3.27−3.31 (m, 2H), 3.38−3.41 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.1 (C4), 27.2 (C3), 28.5 (Boc), 35.5 (b, C7/11), 36.4 (C5), 39.5 (b, C8/10), 40.7 (C2), 49.4 (C6), 79.2 (C−O), 155.0 (CO). HRMS (ESI): calcd for (M + H$^+$) $C_{14}H_{26}N_2O_2$ 255.2067, found 255.2068.

1-Benzyl-1,9-diazaspiro[5.5]undecane (21). Compound **18** (3.68 g, 10.5 mmol) and K_2CO_3 (7.29 g, 52.8 mmol, 5 equiv) was dissolved in methanol (50 mL) and water (50 mL). The reaction mixture was heated for 2.5 h at 90 °C. Benzyl bromide (2 mL, 16.8 mmol) was added dropwise at room temperature. The reaction mixture was stirred overnight at room temperature, and then the methanol was evaporated. The aqueous layer was extracted with DCM (3 × 50 mL). The organic layer was washed with water (2 × 50 mL), dried with $MgSO_4$, and then evaporated to dryness. The product was purified by flash chromatography on silica (DCM, 1% MeOH) to give the spiro compound **20** (2.49 g, 89%) as a pale yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.48−1.70 (m, 17H), 1.87−1.91 (m, 2H), 2.55−2.57 (m, 2H), 3.13−3.18 (m, 2H), 2.65 (s, 2H), 3.80 (bs, 2H), 7.21−7.37 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.4 (C4), 24.0 (C3), 28.7 (Me), 31.7 (b, C7/11), 40.2 (b, C8/10), 46.0 (C2), 51.9 (benzyl CH_2), 54.1 (C6), 79.5 (C−O), 126.7, 128.4 (Ph), 155.2 (CO). LRMS (ESI): calcd for (M + H$^+$) $C_{21}H_{32}N_2O_2$ 345, found 345. Compound **20** (2.49 g, 7.23 mmol) was dissolved in DCM (110 mL) under N_2. TFA (6.6 mL, 88.8 mmol) was added dropwise at 0 °C. The mixture was stirred for 2 h at 0 °C and then overnight at room temperature. The reaction mixture was evaporated to dryness. The crude product was dissolved in toluene (50 mL) and evaporated twice, then dissolved in water (20 mL) and evaporated to dryness. At this stage, the yellow oil was dissolved in methanol (10 mL) and toluene (20 mL) and then evaporated to dryness to give the trifluoroacetic acid salt of 1-benzyl-1,9-diazaspiro[5.5]undecane (**21**.CF_3COOH, 3.02 g, 88%) as a yellow solid. ^{1}H NMR (500 MHz, $DMSO_d$): δ 1.54 (bs, 3H), 1.73−1.82 (m, 2H), 2.09−2.25 (m, 4H), 2.44−2.48 (m, 1H), 2.90 (bs, 1H), 3.07−3.14 (m, 3H), 3.31−3.33 (bs, 2H), 4.11 (bs, 1H), 4.55−4.58 (m, 1H), 7.40−7.48 (m, 5H): 8.89 (bs, 1H), 9.17 b(s, 1H), 9.65 (bs, 1H).^{13}C NMR (125 MHz, $DMSO_d$): δ 17.4 (C4), 20.8 (C3), 25.0 (C5), 27.0 (C7/11), 32.0 (C8/10), 46.1 (C2), 51.6 (benzyl), 63.0 (C6), 117.4 (q, J = 296 Hz, CF_3), 129.4, 130.1, 130.8, 132.0 (benzyl), 159.1 (q, J = 34 Hz, CO). HRMS (ESI): calcd for (M + H$^+$) $C_{16}H_{24}N_2$ 245.2012, found 245.2008.

{The trifluoroacetic acid salt can be converted to the free base by passage through a column of basic alumina (DCM, 2% MeOH, 0.5%NH_3) to give 1-benzyl-1,9-diazaspiro[5,5]undecane (**21**, 89% from **20**) as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.46−1.69 (m, 8H), 1.84−1.88 (m, 2H), 2.54−2.56 (m, 2H), 2.63 (bs, 1H), 2.78−2.82 (m, 2H), 2.98−3.02 (m, 2H), 3.69 (s, 2H), 7.20−7.23 (m, 1H), 7.19−7.22 (m, 2H), 7.27−7.28 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.4 (C4), 24.7 (C3), 32.0 (C5), 32.7

(C7/11), 43.0 (C8/10), 46.2 (C2), 52.1 (benzyl), 54.3 (C6), 126.5, 128.3, 128.35, 142.2 (benzyl). LRMS (ESI): calcd for (M + H^+) $C_{16}H_{24}N_2$ 245, found 245.}

1-Benzoyl-1,9-diazaspiro[5.5]undecane Hydrochloride (22). A solution of 1-benzyl-4-piperidone (**8**, 18.9 g, 100 mmol), allylamine (30.0 mL, 400 mmol), and potassium carbonate (27.6 g, 200 mmol) in toluene (150 mL) was heated at 60 °C, under nitrogen, for 18 h. The reaction mixture was cooled and filtered through a Buchner funnel with fritted disk. The residues were washed with fresh toluene (3 × 50 mL), and the solvent from the combined filtrates was removed in vacuo. The residue was dissolved in dry toluene (150 mL), the solution cooled to 5 °C, and 1 M allylmagnesium bromide in diethyl ether (110 mL, 110 mmol) added, slowly, under an atmosphere of nitrogen. The resulting mixture was allowed to warm to room temperature and stirred for 2.5−3 h. Hydrochloric acid (1 M, 300 mL, 300 mmol) was then added, and the phases were separated. The aqueous phase was basified with 28% ammonium hydroxide solution and extracted with chloroform (3 × 100 mL). The organic phase was dried ($MgSO_4$) and filtered and the solvent removed in vacuo to give the diallyl derivative **13** (24.80 g, 92%) of sufficient purity for the following step. To compound **13** (24.80 g, 91.7 mmol) in toluene (225 mL) was added benzoyl chloride (12.00 mL, 103 mmol) and the resulting solution heated at reflux for 18 h. The reaction mixture was cooled and filtered through a plug of amino bonded silica (100 g) and the residue eluted with DCM (3 × 100 mL). The solvent was removed from the filtrate in vacuo and the residue purified by flash chromatography using methanol/dichloromethane (1/9) to give *N*-benzoyl-**10** (22.43 g, 65%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.26 (m, 2H), 2.36 (m, 2H), 2.45 (m, 2H), 2.67 (m, 2H), 2.97 (d, J = 7.5 Hz, 2H), 3.58 (s, 2H), 3.89 (d, J = 5.5 Hz, 2H), 5.00−5.19 (m, 4H), 5.76 (m, 1H), 5.87 (m, 1H), 7.29−7.36 (m, 10H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 33.6 (C3/5), 37.4 (4-allyl), 50.1 (N-allyl), 50.2 (C2/6), 61.6 (C4), 63.2 (benzyl), 116.5 (4-allyl), 118.5 (*N*-allyl), 126.4, 127.3, 128.48, 128.51, 129.1, 129.5 (benzyl), 134.4 (4-allyl), 137.4 (*N*-allyl), 138.2, 139.8 (benzyl), 174.2 (CO). LRMS (ESI): calcd for (M + H^+) $C_{25}H_{30}N_2O$ 375, found 375.

To a solution of *N*-benzoyl-**10** (19.65 g, 52.5 mmol) in dichloromethane (200 mL) was added Grubbs I catalyst (4.5 g), and the resulting solution was stirred for 48 h. Amino-bonded silica (45 g) was added, the mixture was then filtered through a plug of amino-bonded silica (250 g), and the residues were eluted with dichloromethane (6 × 200 mL). The solvent was removed from the filtrate in vacuo and the residue purified by flash chromatography using methanol/dichloromethane (1/9) to give the 1-*N*-benzoyl analogue of **14** [1-benzoyl-9-benzyl-1,9-diazaspiro[5.5]undec-3,4-ene] (16.47 g, 91%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.86 (br s, 2H), 2.35 (bs, 2H), 2.47 (m, 2H), 2.83 (m, 4H), 3.70 (s, 2H), 3.79 (m, 2H), 5.50 (m, 1H), 5.77 (m, 1H), 7.37 (m, 10H). ^{13}C NMR (CD_3OD, 125 MHz): δ 33.4 (C7/11), 34.9 (C5), 47.4 (C2), 48.9 (C8/10), 55.6 (C6), 62.5 (benzyl), 124.2 (C2), 124.9 (C4), 127.3, 127.5, 128.0, 128.5, 129.9, 130.5, 136.2, 138.1 (benzyl), 174.9 (CO). LRMS (ESI): calcd for (M + H^+) $C_{23}H_{26}N_2O$ 347, found 347.

To solution of 1-benzoyl-9-benzyl-1,9-diazaspiro[5.5]undec-3,4-ene (25.63 g, 73.98 mmol) in methanol (1 L) were added acetyl chloride (5.26 mL, 73.98 mmol) and 10% palladium on carbon (12 g), and the mixture was evacuated and flushed three times with hydrogen. The reaction mixture was stirred under an atmosphere of hydrogen until the reaction was complete. The mixture was filtered through Celite, and the residues were washed with methanol (3 × 200 mL). Most of the solvent was removed from the combined filtrate in vacuo and toluene (50 mL) added. The product was precipitated by the addition of dry ether, collected by decanting and washing with ether, and dried under vacuum to give the hydrochloride salt of 1-benzoyl-1,9-diazaspiro[5,5]undecane (**22**·HCl, 19.65 g, 90%) as a white solid. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 1.41 (m, 2H), 1.64 (m, 2H), 1.72 (m, 4H), 3.03 (m, 4H), 3.11 (m, 2H), 3.31 (m, 2H), 7.46 (s, 5H), 8.90 (br s, 1H), 9.31 (br s, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 18.6 (C4), 25.6 (C3), 30.5 (C5), 33.5 (C7/11), 40.4 (C8/10), 45.7 (C2), 56.5 (C6), 127.7, 129.2, 130.6, 139.1 (Ph), 173.8 (CO). HRMS (ESI): calcd for (M + H^+) $C_{16}H_{23}N_2O$ 259.1805, found 259.1809. IR: ν 1636 cm^{-1}.

9-Benzoyl-1,9-diazaspiro[5.5]undecane Hydrochloride (23). A solution of **22** (15.24 g, 51.7 mmol) in dichloromethane (100 mL) was treated with amino-bonded silica (150 g) and filtered, and the silica was washed with dichloromethane (3 × 100 mL). The solvent was removed from the filtrate in vacuo, and the residue was heated neat at 70 °C for 1 week. The residue was purified by flash chromatography on neutral alumina using chloroform. The purified product was dissolved in methanol and converted to the salt by addition of methanolic hydrogen chloride. Toluene was then added and the solvent removed in vacuo to give the hydrochloride salt of 9-benzoyl-1,9-diazaspiro[5.5]undecane (**23**·HCl) as a light tan solid (11.96 g, 78%). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.58 (br s, 2H), 1.68 (m, 2H), 1.79 (m, 2H), 1.88 (br s, 4H), 3.00 (br s, 2H), 3.30 (br s, 2H), 3.53 (br s, 1H), 4.11 (br s, 1H), 7.37 (m, 2H), 7.47 (m, 3H), 9.34 (br s, 2H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 18.0 (C4), 22.3 (C3), 30.3 (C5), 32.4 (b, C7/11), 37.4 (C8), 39.1 (C2), 43.1 (C10), 55.7 (C6), 127.3, 129.2, 130.3, 136.6 (Ph), 169.7 (CO); (125 MHz, $CDCl_3$): δ 18.2 (C4), 22.2 (C3), 31.4 (C5), 33.0 (C7/11), 37.4 (b, C8), 39.8 (C2), 43.0 (b, C10), 56.1 (C6), 127.2, 128.8, 130.1, 135.6 (Ph), 170.7 (CO). HRMS (ESI): calcd for (M + H^+) $C_{16}H_{23}N_2O$ 259.1805, found 259.1811. IR: ν 1611 cm^{-1}.

***tert*-Butyl 3,7-Diazaspiro[5.6]dodecane-3-carboxylate Hydrochloride (29).** 1-Benzyl-4-piperidone (**5**, 51.48 g, 0.272 mol) was dissolved in toluene (300 mL). K_2CO_3 (112.78 g, 0.816 mol) was added followed by 3-butenylamine hydrochloride (29.104 g, 0.272 mol, prepared from 3-buten-1-ol by mesylation, displacement with trifluoroacetamide in the presence of potassium carbonate in refluxing toluene, followed by deacylation with potassium carbonate in methanol). The mixture was stirred at 60 °C for 20 h. After cooling, the mixture was filtered through diatomaceous earth and concentrated to dryness to afford the corresponding imine as a brown oil (64.21 g, 98%). The crude imine (64.21 g, 0.265 mol) was dissolved in toluene (250 mL) and cooled in an ice bath under N_2. Allylmagnesium bromide in diethyl ether (265 mL, 0.265 mol) was added and the mixture was stirred overnight while warming to room temperature. The mixture was then cooled back down to 0 °C and acidified with 1 M HCl to ∼pH 2. The toluene layer was separated, and the aqueous layer was treated with solid K_2CO_3 (∼pH 12). The organic material was extracted into $CHCl_3$ (7 × 200 mL), dried ($MgSO_4$), filtered, and concentrated to afford the butenylamine analogue of **10** as a red oil (61.55 g, 82%). Without purification, a portion of the red oil (18.46 g, 0.065 mol) was dissolved in CH_2Cl_2 (250 mL) and cooled to −78 °C. Trifluoroacetic anhydride (13.597 mL, 0.098 mol) was added dropwise and the mixture stirred overnight while warming to room temperature. CH_2Cl_2 (200 mL) was added and the mixture washed with saturated $NaHCO_3$ (2 × 200 mL) and H_2O (2 × 200 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated. The product was chromatographed on a SiO_2 column eluting with Hex/EtOAc (4:1) to afford the diene **26** as a red/orange oil (20.70 g, 84%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.07 (m, 2H), 2.23−2.44 (m, 6H), 2.74 (m, 2H), 2.87 (m, 2H), 3.38 (m, 2H), 3.54 (s, 2H), 5.07−5.19 (m, 4H), 5.64−5.74 (m, 2H), 7.28−7.39 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 33.0, 34.0, 37.3, 43.9, 49.0, 63.1, 63.9, 116.8 (q, J = 288 Hz, CF_3), 117.8, 119.2, 127.4, 128.5, 129.3, 129.4, 131.0, 132.9, 133.7, 157.5 (q, J = 40 Hz, CO). LRMS (ESI): calcd for (M + H^+) $C_{21}H_{27}F_3N_2O$ 381, found 381.

The diene **26** (49.94 g, 0.131 mol) was dissolved in CH_2Cl_2 (300 mL) and degassed. Grubbs first-generation catalyst (10.78 g, 13.1 mmol, 10 mol %) was added, and the reaction was stirred at room temperature for 48 h. A second batch of Grubbs first-generation catalyst (5.39 g, 6.55 mmol, 5 mol %) was added, and the reaction was stirred for another 24 h. The solvent was then removed, and the crude material was flushed through a plug of amino-bonded SiO_2. The crude material was concentrated to dryness to afford

3-benzyl-7-trifluoroacetyl-3,7-diazaspiro[5.6]dodec-10-ene (**27**) as a brown oil (41.04 g, 89%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.57 (m, 2H), 2.30 (m, 2H), 2.41 (bs, 2H), 2.68 (m, 4H), 3.04−3.10 (m, 2H), 3.57 (s, 2H), 3.81 (m, 2H), 5.61 (m, 1H), 5.66 (m, 1H), 7.25−7.38 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 29.9 (C9), 31.7 (C12), 33.4 (C1/5), 42.1 (C8), 50.2 (C2/4), 62.4 (benzyl), 67.0 (C6), 116.9 (q, J = 288 Hz, CF_3), 124.5 (C10), 127.2 (C11), 128.4, 129.2, 129.7, 138.6 (benzyl), 157.3 (q, J = 34 Hz, CO). LRMS (ESI): calcd for (M + H$^+$) $C_{19}H_{23}F_3N_2O$ 353, found 353.

Without further purification, compound **27** (70.05 g, 0.19 mol) was dissolved in MeOH (1 L) and H_2O (200 mL) added. NaOH (39.8 g, 0.995 mol) was added, and the mixture was refluxed for 72 h. After cooling, the solvent was removed and the solution acidified with HCl. The mixture was then washed with $CHCl_3$ (100 mL) and the aqueous layer separated and made basic with K_2CO_3. The organic compound was extracted into $CHCl_3$ (5 × 200 mL), which was dried over anhydrous $MgSO_4$, filtered, and evaporated to give 38.16 g of a dark oil. The oil was then dissolved in MeCN (600 mL) and stirred with $(Boc)_2O$ (65.04 g, 0.298 mol) for 16 h. The solvent was then removed, and the residue was washed with satd $NaHCO_3$ (250 mL) and extracted into $CHCl_3$ (3 × 200 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated to dryness to afford *tert*-butyl 3-benzyl-3,7-diazaspiro[5.6]dodecane-3-carboxylate as a brown oil (50.98 g, 75%). Without purification, the brown oil (49.43 g, 0.139 mol) was dissolved in MeOH (1.0 L), 10% Pd−C (49.43 g) was added, and the mixture was stirred under a H_2 atmosphere for 96 h. The mixture was filtered through diatomaceous earth, and the solvent was removed to afford 22.19 g of a pale yellow oil. This was suspended in diethyl ether (100 mL). HCl in diethyl ether/dioxane was added until a pale yellow solid dropped out. The solid was filtered and dried to afford **28** (11.85 g, 49%) (loss of the Boc protecting group at this stage was unexpected; clearly, too much HCl was added. It is recommended that if the 7-Boc analogue of **29** is desired the product obtained after hydrogenolysis be purified directly on neutral alumina). Compound **28** (11.85 g, 49 mmol) was redissolved in MeOH (250 mL) and cooled to 0 °C. $(Boc)_2O$ (10.77 g, 49 mmol) was added followed by K_2CO_3 (6.77 g, 0.049 mol). After the mixture was stirred for 1 h, the solvent was removed and the paste obtained was dissolved in diethyl ether (50 mL) and washed with H_2O (50 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and reduced to give 11.563 g (87%) of *tert*-butyl 3,7-diazaspiro[5.6]dodecane-7-carboxylate (**29**) as a brown oil. A small ample of the brown oil (1 g) was purified by chromatography on silica gel, eluting with 5% MeOH/$CHCl_3$, to give **29** (0.25 g, 25%; the low yield was possibly due to partial loss of the Boc group on the column) as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.3−1.6 (m, 21H), ∼2.0 (vbs, 1H), 2.68−2.73 (m, 2H), 3.26−3.36 (m, 2H), 3.45−3.55 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.5 (C11), 28.7 (Boc), 30.3 (C10), 33.7 (C9), 37.6 (b, C1/5), 40.3 (b, C2/4), 41.0 (C13), 42.1 (C8), 53.3 (C6), 79.5 (C−O), 155.3 (CO). [It should be noted that if the $CDCl_3$ contains any HCl, both ^{1}H and ^{13}C chemical shifts change significantly]. HRMS (ESI): calcd for (M + H$^+$) $C_{15}H_{29}N_2O_2$ 269.2223, found 269.2231.

(±)-1,8-Dibenzyl-3-bromo-1,8-diazaspiro[5.6]decane (32). 1-Benzyl-4-piperidone (**8**, 15.0 g, 80.0 mmol) was dissolved in toluene (100 mL). K_2CO_3 (22.1 g, 160 mmol) was added followed by benzylamine (11.4 mL, 104 mmol). The mixture was stirred at 60 °C for 16 h. After cooling, the material was filtered through diatomaceous earth and concentrated to dryness to afford the imine **30** as an orange oil (23.99 g, 97%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.55 (m, 4H), 2.60 (m, 2H), 2.70 (m, 2H), 3.60 (s, 2H, 4-benzyl), 4.58 (s, 2H, 1-benzyl), 7.28−7.38 (m, 10H, ArH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 29.3 (C3), 39.3 (C5), 53.5 (4-benzyl), 54.5 (C2/6), 62.7 (1-benzyl), 126.9, 127.3, 128.0, 128.6, 128.7, 129.2, 138.7, 140.5 (benzyl), 171.2 (*C*═N). The imine **30** (23.99 g, 78.0 mmol) was dissolved in toluene (185 mL) and cooled in an ice bath. Allylmagnesium bromide (78.0 mL, 78.0 mmol) was added, and the mixture was stirred for 16 h while warming to room temperature. The mixture was then recooled in an ice bath, and 1 M HCl was used to adjust the pH to approximately 1. The toluene layer was then removed, and the aqueous layer was made basic with K_2CO_3 (pH ∼12). The aqueous layer was extracted with $CHCl_3$ (5 × 30 mL), which was dried ($MgSO_4$), filtered, evaporated, and chromatographed on a SiO_2 column, eluting with CH_2Cl_2/MeOH (9:1) to afford the allyl derivative **31** as a yellow oil (22.99 g, 92%). ^{1}H NMR δ (500 MHz, $CDCl_3$): 1.67 (m, 4H), 2.30 (m, 2H), 2.55 (m, 4H), 3.57 (s, 2H, benzyl), 3.68 (s, 2H, benzyl), 5.16 (m, 2H), 5.90 (m, 1H), 7.27−7.40 (m, 10H, ArH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 35.4 (C3/5), 42.5 (allyl), 45.6 (C4), 49.6 (C2/6), 52.6 (4-benzyl), 63.6 (1-benzyl), 118.1 (allyl), 127.1, 127.2, 128.5, 128.6, 128.62, 129.5 (benzyl), 134.4 (allyl), 139.0, 141.8 (benzyl). Compound **31** (22.99 g, 72.0 mmol) was dissolved in MeOH (30 mL) and cooled to 0 °C. In a separate flask, AcBr (13.41 mL, 180 mmol) was added to MeOH (30 mL). The contents were then added to the first flask. After the mixture was stirred for 20 min, the solvent was removed to afford an off-white foam. Dry CH_2Cl_2 (1038 mL) and MeOH (112 mL) were added and the mixture was cooled to −78 °C. Bromine (5.53 mL, 108 mmol, 1.5 eq) was added and the mixture was stirred for 3 h (LRMS taken of solution at this point, *m*/*z* 479.1/481.1/483.1). The mixture was then cooled to 0 °C and K_2CO_3 (19.90 g, 144 mmol) was added followed by H_2O (50 mL). The mixture was stirred for 16 h while warming to room temperature. The mixture was then washed with sat. $Na_2S_2O_3$ (1 × 250 mL), sat. K_2CO_3 (1 × 300 mL) and H_2O (1 × 300 mL), dried ($MgSO_4$), filtered and concentrated to dryness. The compound was purified on a SiO_2 column eluting with CH_2Cl_2/MeOH (95:5) to afford (±)-1,8-dibenzyl-3-bromo-1,8-diazaspiro[5.6]decane (**32**) as a red/orange oil/gum (25.81 g, 90%). ^{1}H NMR δ (500 MHz, $CDCl_3$): 1.26 (m, 1H, H6a), 1.63 (m, 1H, H10a), 1.94−2.08 (m, 4H, H6b, H7b, H9b, H10b), 2.16 (dd, J = 5, 14.5 Hz, 1 H, H4b), 2.35 (dd, J = 8.5, 14.5 Hz, 1H, H4a), 2.88 (m, 2H, H7a, 9a), 2.89 (dd, J = 6, 10.5 Hz, 1H, H2b), 3.07 (dd, J = 6, 10.5 Hz, H2a), 3.49 (s, 2H, CH_2Ph), 3.57 (d, J = 13.5 Hz, CH_aPh), 3.66 (d, J = 13.5 Hz, CH_bPh), 4.21 (m, J = 5, 6, 8.5, 12 Hz, 1H, H3), 7.12−7.28 (m, 10H, ArH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 32.4 (C6), 33.5 (C10), 43.78 (C3), 46.9 (C4), 51.6 (C2), 51.7 (C7), 51.8 (C9), 60.2 (1-benzyl), 62.4 (8-benzyl), 63.3 (C5), 127.1, 127.6, 128.5, 128.6, 128.7, 129.6, 137.5, 140.4 (benzyl). LRMS: *m*/*z* 399/401 [M + H]$^+$. HRMS (ESI): calcd for (M + H$^+$) $C_{22}H_{28}{}^{79}BrN_2$ 399.1430, found 399.1432.

***tert*-Butyl 1,8-Diazaspiro[5.6]decane-8-carboxylate (34).** Compound **32** (25.81 g, 65 mmol) was dissolved in isopropanol (700 mL). $(Boc)_2O$ (12.66 g, 58 mmol) was added followed by 10% Pd−C (25.81 g). The mixture was stirred under a hydrogen atmosphere while heating to 75 °C. After 48 h, the mixture was cooled and filtered through diatomaceous earth. The solvent was removed affording 18.67 g of an orange foam. This was suspended in diethyl ether (50 mL) and acidified to ∼pH 5 with satd NH_4Cl. The diethyl ether layer was removed, and the aqueous layer was washed with diethyl ether (2 × 50 mL) again. The aqueous layer was then made basic with 1 M NaOH, and the organic compound was extracted into CH_2Cl_2 (3 × 100 mL). The chloroform layer was dried ($MgSO_4$), filtered, and concentrated to dryness to afford *tert*-butyl 1,8-diazaspiro[5.6]decane-8-carboxylate (**34**) as a brown/yellow oil (5.85 g, 38%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.39 (s, 9H, Boc), 1.40−1.49 (m, 4H, H6/10), 1.50 (m, 2H, H4), 1.72 (m, 2H, H3), 2.89 (m, 2H, H2), 3.28 (m, 2H, H7a/9a), 3.43 (m, 2H, H7b/9b), 4.11 (br s, 1H, NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 25.5 (C3), 28.6 (Boc), 36.8 (C4), 37.6 (b, C6/10), 41.7 (b, C7/9), 45.7 (C2), 60.1 (C5), 79.4 (C−O), 155.0 (CO). HRMS (ESI): calcd for (M + H$^+$) $C_{13}H_{25}N_2O_2$ 241.1911, found 241.1922.

***tert*-Butyl 1-Amino-7-azaspiro[3.5]nonane-7-carboxylate Hydrochloride (43).** To a solution of *tert*-butyl 1-oxo-7-azaspiro[3,5]-nonane-7-carboxylate[29] (**42**, 8 g, 33.5 mmol) in anhydrous 1,2-dichloroethane (230 mL) was added benzylamine (3.93 g, 36.8 mmol, 1.1 equiv) followed by sodium triacetoxyborohydride (15.5 g, 73.6 mmol, 2 equiv). The mixture was stirred at rt for 18 h and

then quenched with saturated aqueous sodium bicarbonate and the product extracted with chloroform (3 × 200 mL). The combined extracts were washed with water (2 × 200 mL) and brine (2 × 100 mL), dried through a phase-separating paper, and concentrated to dryness. The product was purified by silica gel chromatography eluting with 5% MeOH/DCM to give *tert*-butyl 1-(benzylamino)-7-azaspiro[3.5]nonane-7-carboxylate (10 g, 88%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.30−1.40 (m, 12H), 1.55−1.80 (m, 4H), 2.08 (m, 1H), 2.62 (m, 1H), 2.80 (m, 1H), 2.97 (m, 1H), 3.70 (s, 2H), 3.80 (m, 1H), 3.95 (m, 1H), 7.20−7.30 (m, 5H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 25.2 (C2), 25.4 (C3), 28.7 (Boc), 29.2 (C5), 38.8 (C9), 41.0 (b, C6/8), 43.6 (C4), 52.1 (benzyl), 60.7 (C1), 79.5 (C−O), 127.3, 128.4, 128.6, 140.0 (benzyl), 155.1 (CO). LRMS (ESI): calcd for (M + H$^+$) $C_{20}H_{31}N_2O_2$ 331, found 331.

To a solution of *tert*-butyl 1-(benzylamino)-7-azaspiro[3.5]nonane-7-carboxylate (8.5 g, 25.7 mmol) in methanol (200 mL) was added 20% $Pd(OH)_2$/C (5 g) in one lot. The reaction mixture was stirred at rt under a hydrogen atmosphere (balloon) for 20 h, and then the catalyst was filtered off through a Celite-packed funnel. The celite layer was washed with fresh methanol (3 × 100 mL). The combined filtrate and washings were concentrated. The residue was diluted with water (25 mL) and acidified with a solution of citric acid (20%, pH 5). The acidified aqueous solution was extracted with chloroform (3 × 100 mL) to remove impurities. The aqueous fraction was then basified with a solution of sodium hydroxide (2 M, pH 8−9). The free amine was extracted with chloroform (3 × 100 mL), concentrated, and dried under reduced pressure to give *tert*-butyl 1-amino-7-azaspiro[3.5]nonane-7-carboxylate (5.88 g, 95%) as a colorless oil.^{1}H NMR (CD_3OD, 500 MHz): δ 1.45 (s, 9H), 1.40−1.65 (m, 5H), 1.75 (m, 2H), 2.20 (m, 1H), 2.85 (m, 1H), 3.00 (m, 1H), 3.04 (m, 1H), 3.83 (m, 1H), 3.94 (m, 1H), 4.80 (m, 2H). ^{13}C NMR (CD_3OD, 125 MHz): δ 26.4 (C2), 27.4 (C3), 28.7 (Boc), 29.9 (C5), 38.5 (C9), 41.7 (b, C6/8), 44.4 (C4), 56.2 (C1), 80.8 (C−O), 156.6 (CO). LRMS (ESI): calculated for (M+H$^+$) $C_{13}H_{25}N_2O_2$ 241, found 241. The oil was converted into the hydrochloride salt: to an ice-cold solution of *tert*-butyl 1-amino-7-azaspiro[3.5]nonane-7-carboxylate (5.88 g, 24.5 mmol) in anhydrous diethyl ether (50 mL) was added dropwise hydrogen chloride in ether (12.25 mL, 2 M, 1 equiv). A white precipitate formed quickly. After addition of the hydrogen chloride, a further amount of dry ether (50 mL) was added. The precipitate was filtered and washed with dry ether (3 × 100 mL), then dried under vacumm overnight to give the crude product (5.5 g, 81%) as a white solid. The white solid (5.5 g) was dissolved in the minimum amount of methanol (3 mL) to give a clear solution. To this stirred solution was added anhydrous ether until a white precipitate formed. After 5 min, more ether was added (100 mL), followed by one more addition (50 mL). The white solid was filtered and washed with dry ether. The solid was dried under vacuum to give *tert*-butyl 1-amino-7-azaspiro[3.5]nonane-7-carboxylate hydrochloride (**43**, 4.1 g, 60%). ^{1}H NMR (CD_3OD, 500 MHz): δ 1.45 (s, 9H), 1.50 (m, 1H), 1.63 (m, 2H), 1.78 (m, 2H), 2.04 (m, 2H), 2.35 (m, 1H), 2.78 (m, 1H), 2.92 (m, 1H), 3.30 (MeOH - used as reference), 3.45 (m, 1H), 3.90 (m, 1H), 4.01 (m, 1H). ^{13}C NMR (D_2O, 125 MHz): d 22.2 (C2), 26.0 (C3), 28.6 (Boc - used as reference), 29.6 (C5), 36.9 (C9), 40.6 (b, C6), 41.5 (b, C8), 41.8 (C4), 53.2 (C1), 82.7 (C−O), 157.5 (CO). HRMS (ESI): calcd for (M + H$^+$) $C_{13}H_{25}N_2O_2$ 241.1911, found 241.1919.

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Supporting Information Available: General experimental procedures, experimental data for **42**, and ^{1}H and ^{13}C NMR spectra for the scaffolds **15**, **17**, **19**, **21**−**23**, **29**, **32**, **34**, and **43**. This material is available free of charge via the Internet at http://pubs.acs.org.

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