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Synthesis of a Family of Spirocyclic Scaffolds: Building Blocks for the Exploration of Chemical Space

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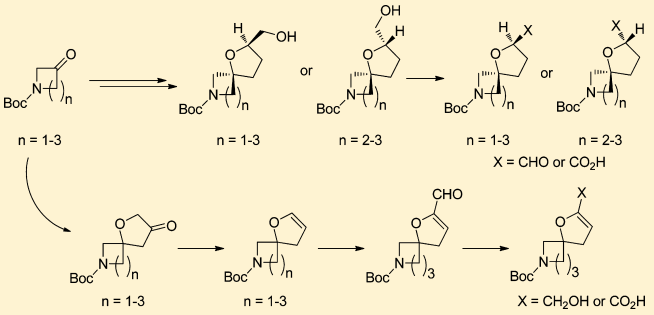
Supporting Information

ABSTRACT: This report describes the preparation of a series of 17 novel racemic spirocyclic scaffolds that are intended for the creation of compound libraries by parallel synthesis for biological screening. Each scaffold features two points of orthogonal diversification. The scaffolds are related to each other in four ways: (1) through stepwise changes in the size of the nitrogen-bearing ring; (2) through the oxidation state of the carbon-centered point of diversification; (3) through the relative stereochemical orientation of the two diversification sites in those members that are stereogenic; and (4) through the provision of both saturated and unsaturated versions of the furan ring in the scaffold series derived from 3-piperidone. The scaffolds provide incremental changes in the relative orientation of the diversity components that would be introduced onto them. The scaffolds feature high sp^3 carbon content which is essential for the three-dimensional exploration of chemical space. This characteristic is particularly evident in those members of this family that bear two stereocenters, i.e., the two series derived from 3-piperidone and 3-pyrrolidinone. In the series derived from 3-piperidone we were able to "split the difference" between the two diastereomers by preparation of their corresponding unsaturated version.



INTRODUCTION

The exploration of chemical space is often invoked by workers in high-throughput synthesis as a goal in library design. Chemical space can be envisioned as the microscopic volume enveloping a molecule. As a molecule undergoes dynamic changes the envelope follows. Flexible molecules have flexible space, whereas rigid molecules have more static space.

The latter case enables controlled explorations of the relationship between spatial placement and molecular properties. Static space can be surveyed by introducing incremental changes into a well-defined molecule at its core, or scaffold, which orients its peripheral substituents. The relative placement of peripheral substituents, both to the scaffold and each other, determines the molecule's properties. Diversity in compound libraries generally includes variation of substituents around a scaffold, imparting certain characteristics such as degrees of lipophilicity or hydrophilicity. Carefully choosing the peripheral elements reveals the effect of their associated properties and placement on the properties of the molecule.

Spirocycles are ideal for this purpose. These molecules feature structural complexity with incrementally variable placement of substituents.[1,2] Accessible carbons can serve as a "hinge" for "swinging" substituents in localized arcs as illustrated in Figure 1. A substituent X can be oriented above, below or, in the unsaturated case, within the plane of the page.

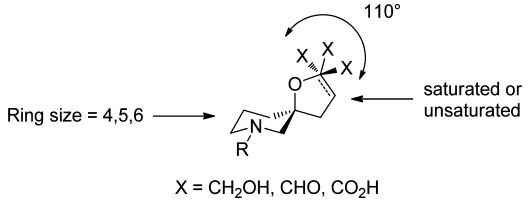


Figure 1. Representation of a family of spirocyclic scaffolds.

This is analogous to a door which rests on hinges. The wall to which the hinges are attached is rigid while the hinges serve as the point of flexibility. The three positions shown in Figure 1 define an arc of about 110° at the extremes and are distinct if the spiro carbon is stereogenic. Synthesis of all three variations will reveal the effect on this molecule's properties of swinging X through the arc.

Our goal was to prepare a family of related novel spirocyclic scaffolds that would offer the opportunity to effect incremental changes in the molecular architecture of derived compound libraries. We were attracted to the idea that scaffolds having a high proportion of saturated (sp^3) carbons would enable the

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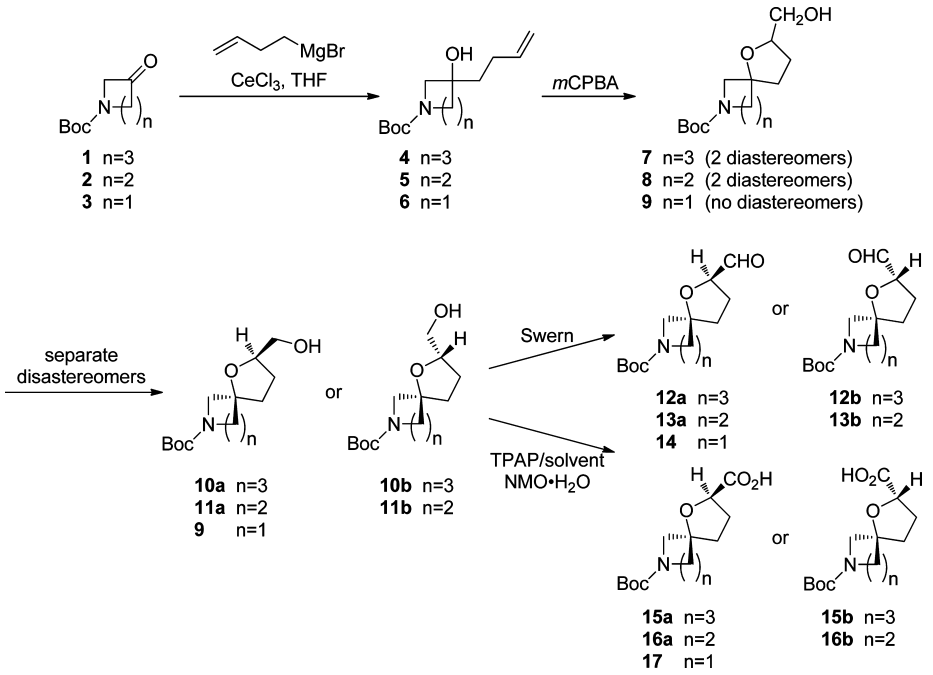
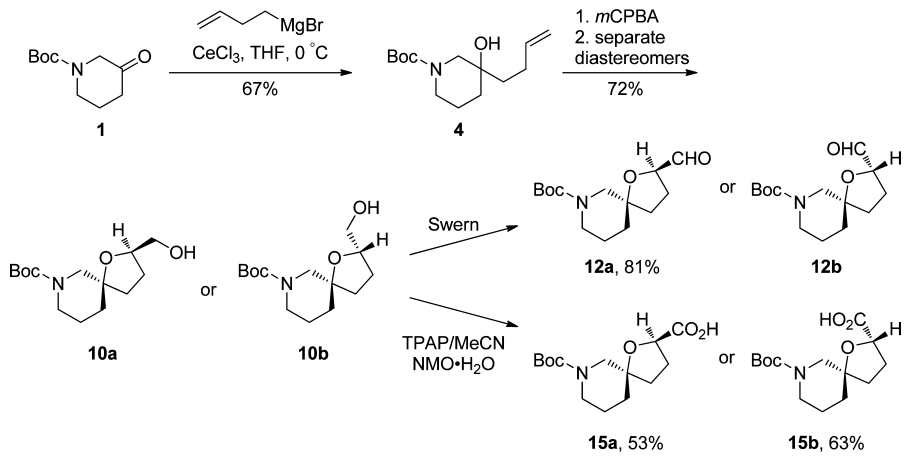
Scheme 1. General Synthesis Scheme of Racemic Spiro-THF Scaffolds from *N*-Boc-Protected Cyclic 2-Aminoketones



Scheme 2. Racemic Spiro-THF Scaffolds Derived from *N*-Boc-3-piperidone 1



exploration of three-dimensional space.[3] We chose 1-Boc-3-piperidone at the outset: first, because spirocyclization creates a stereocenter and, second, in searching the online literature we found that simple spirocyclic derivatives of 3-piperidone are relatively uncommon, especially when compared to those derived from 4-piperidone. This report details our work toward deriving both saturated and unsaturated spirocyclic scaffolds that correspond to those shown in Figure 1 from protected 2-*N*-substituted cyclic ketones like 1-Boc-3-piperidone and its lower homologues.

RESULTS AND DISCUSSION

Spirocyclic Tetrahydrofuran (THF) Scaffolds Derived from *N*-Boc-Protected Cyclic 2-Aminoketones. All spiro-THF scaffolds were constructed from *N*-Boc-protected cyclic 2-aminoketones as shown in Scheme 1. The cyclic ketones **1**−**3** were added to homoallyl magnesium bromide[4] that was preexposed to $CeCl_3$ to furnish tertiary alcohols **4**−**6**.[5] Epoxidation with *m*-CPBA, followed by spontaneous epoxide ring-opening via a Baldwin favored 5-exo-tet nucleophilic attack,[6] afforded the racemic spirocyclic THF methanols **7**−**9**.[7] In no case was any evidence observed for the formation of tetrahydropyran products via the alternative 6-endo-tet ring closure mechanism. The diastereomers of **7** and **8** were separated. Further oxidation, under different conditions, of **10a**/**10b**, **11a**/**11b** and **9** afforded the aldehydes **12a**/**12b**, **13a**/**13b** and **14** or the acids **15a**/**15b**, **16a**/**16b** and **17**.[8] The behavior of the three sets of scaffolds was sufficiently distinct that each case is described individually.

Spirocyclic THFs Derived from *N*-Boc-3-piperidone (1). Addition of *N*-Boc-3-piperidone **1** to a preformed mixture of freshly prepared homoallyl Grignard reagent and $CeCl_3$ gave the tertiary alcohol **4** (Scheme 2). In the absence of $CeCl_3$, the Grignard reagent addition to ketone **1** was lower yielding (~25%) with the formation of significant quantities of the reduction product *N*-Boc-3-piperidinol.[9] We were delighted to find that treatment of **4** with *m*-CPBA at ambient temperature spontaneously afforded only the alcohols **7** as a 1:1 mixture of diastereomers. These were readily separated, affording **10a** and

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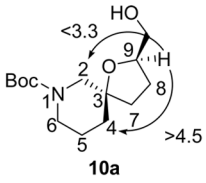
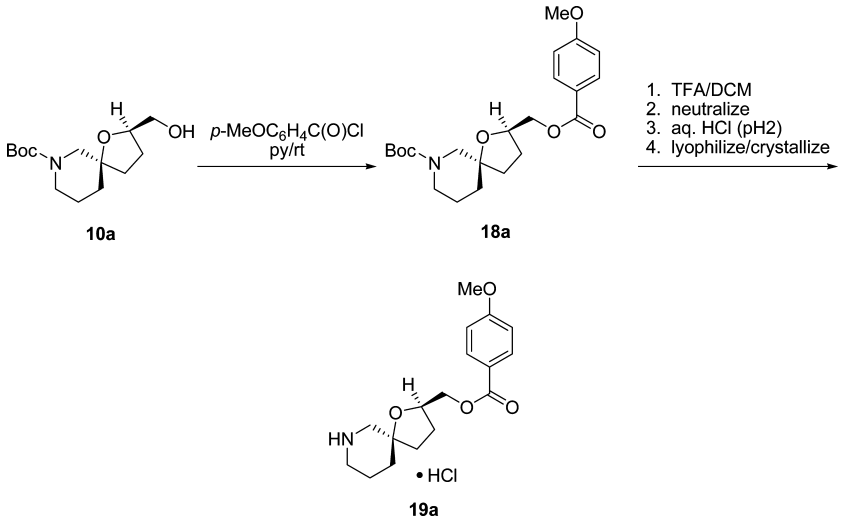


	10a	10b
1H-1H NOESY at frequency corresponding to C2	resonance to H9	no resonance to H9
1H-1H NOESY at frequency corresponding to C4	no resonance to H9	resonance to H9

Figure 2. Distances between H's on C9, C4, and C2 in angstroms as measured by MM2 models.

Scheme 3. Preparation of 19a



10b. The epoxide intermediate was never detected during the reaction by ^{1}H NMR spectroscopy. The relative stereochemistries of **10a** and **10b** were established by correlation NMR spectroscopy and X-ray crystallography as discussed below.

Alcohol **10a** was oxidized to the corresponding aldehyde **12a** or the acid **15a** under different conditions. Alcohol **10b**, under the same conditions, gave evidence (^{1}H NMR spectroscopy of the crude product) of the formation of aldehyde **12b** as expected. However, we were unable to isolate **12b** in satisfactory purity for full characterization purposes. It seemed that **12b** was insufficiently stable to be purified by column chromatography. The acid **15b**, by contrast, was stable and fully characterized. We recommend that aldehyde **12b** be generated and promptly used without column chromatography.

In silico modeling of **10a** and **10b** using the MM2 force field indicates that H9 faces C2 in the former and C4 in the latter (Figure 2). In the model structure for **10a** the ^{1}H−^{1}H distance between H9 and the *pro-S* H2 methylene is less than 3.3 Å, whereas the distance between H9 and either the *pro-R* or *pro-S* H4 methylene is greater than 4.5 Å, leading to the prediction of a strong or medium nuclear Overhauser effect (NOE) between H9 and H2 and a weak or no NOE between H9 and H4 for **10a**. On the other hand, in the model structure for **10b** the ^{1}H−^{1}H distance between H9 and either the *pro-R* or *pro-S* H2 methylene is greater than 4.5 Å, whereas the distance between H9 and the *pro-R* H4 methylene is less than 3.3 Å, leading to the prediction of a strong or medium NOE between H9 and H4 and a weak or no NOE between H9 and H2. On the basis of these observations, through-space interactions measured using NOE were employed in lieu of a dihedral angle-based approach for relative diastereospecific assignment of these spirocycles. Due to spectral overlap it is not possible to unambiguously assign these diastereomers using 1D ^{1}H selective and 2D ^{1}H−^{1}H NOESY at 500 and 800 MHz. Going to higher dimensionality resolves crowded spectra. A 3D ^{1}H−^{13}C−^{1}H HSQC-NOESY spectrum was acquired for **10a** and **10b**. A 2D strip of the 3D data at the ^{13}C frequency corresponding to C2 for **10a** was generated (see the Supporting Information). There was a resonance to H9, indicating that H2 and H9 are close in space for **10a**. The analogous strip for **10b** shows no resonance that can be assigned to H9, indicating that H2 and H9 are not close in space for **10b** (see Supporting Information). 2D strips at the ^{13}C frequency corresponding to C4 for **10a** and **10b**, respectively, were also generated (see Supporting Information). For **10a**, there is no resonance corresponding to H9, indicating that H4 and H9 are not close in space. For **10b**, there is a peak corresponding to H9, indicating that H4 and H9 are close in space. Overall, the 3D HSQC-NOESY indicates convincingly that diastereomers **10a** and **10b** possess the structures shown in Figure 2.

As an additional check on the 3D HSQC-NOESY data, compound **10a** was converted via ester **18a** to the HCl salt **19a** (Scheme 3). Lyophilization of **19a** followed by recrystallization afforded crystals suitable for X-ray diffraction (see Supporting Information, Figure S3), confirming the stereochemical assignment.

Spirocyclic THFs derived from *N*-Boc-3-pyrrolidinone (2). *N*-Boc-3-pyrrolidinone **2** was exposed to homoallyl magnesium bromide in the presence of $CeCl_3$ as described

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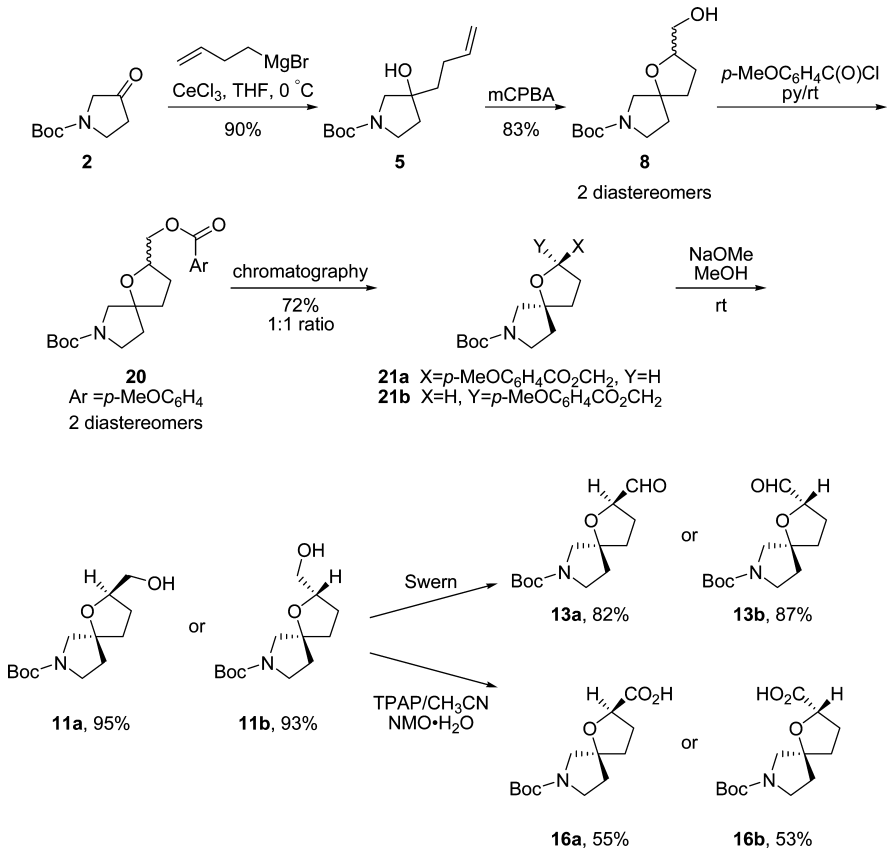
Scheme 4. Racemic Spiro-THF Scaffolds from *N*-Boc-3-pyrrolidinone 2

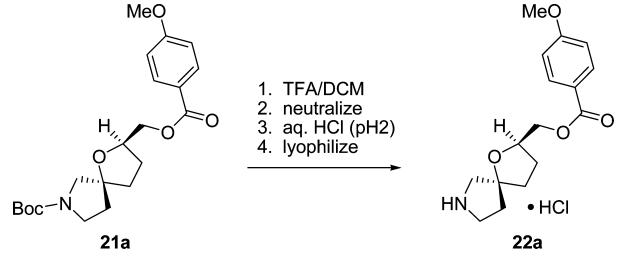


above, giving the tertiary alcohol **5** (Scheme 4). *m*-CPBA treatment of **5** afforded the diastereomers **8** without the intermediate epoxide being detected by ^{1}H NMR spectroscopy. Our attempts to separate diastereomers **8** by various normal or reverse phase chromatographic methods were unsuccessful. Instead, the mixture of diastereomers **8** was converted to the corresponding *p*-OMe-benzoyl esters **20** which were separated by normal phase chromatography, providing the individual diastereomers **21a** and **21b**. Ester hydrolysis regenerated the alcohols as the single diastereomers **11a** and **11b**. Each diastereomer was oxidized to either its corresponding aldehyde **13a** and **13b** or acid **16a** and **16b** as shown.

Aldehydes **13a** and **13b**, under normal handling conditions, gave evidence of instability. The two aldehydes could be prepared and isolated but storage for a few days at rt produced changes in the ^{1}H NMR spectrum that suggested the formation of other unidentified materials. We recommend that aldehydes **13a** and **13b** be used soon after preparation and preferably without column chromatography. Alcohols **11a** and **11b** as well as acids **16a** and **16b** did not show evidence of similar behavior.[10]

The unambiguous assignment of the relative stereochemistry for the two isomers **11a** and **11b** by various 1D, 2D, and 3D NMR experiments could not be made. Instead, ester **21a** was *N*-deprotected and converted to the HCl salt **22a**, which was lyophilized to afford crystals suitable for X-ray crystallography (Scheme 5). Thus, **21a** has the relative stereochemistry shown in Scheme 5 (see the Supporting Information). Its precursor **11a** has the relative stereochemistry shown in Scheme 4, and **11b** has the opposite relative stereochemistry.

Scheme 5. Preparation of 22a



Spirocyclic THFs Derived from *N*-Boc-3-azetidinone (3). *N*-Boc-3-azetidinone **3** was exposed to homoallyl magnesium bromide/$CeCl_3$ as described above to afford the tertiary alcohol **6** (Scheme 6). In this case, we anticipated that the ring strain present in **3** might render the use of cerium less critical than for **1**. The Grignard reagent in the absence of $CeCl_3$ afforded **6** in 53% yield. This yield was better than that obtained using the Grignard alone with **1** but the improvement was insufficient to cause discontinuation of the cerium modification. Epoxidation of **6** afforded the intermediate epoxide (not shown) which, unlike in the cases of **4** and **5**, could be observed, even after 24 h, as a mixture with **9** by ^{1}H NMR spectroscopy (epoxide: δ 2.98−2.88 (m, 1H), 2.77 (dd, J = 4.7. 4.0 Hz, 1H), 2.52 (dd, J = 4.7, 2.8 Hz, 1H)). Aging of the reaction for 48 h was required to achieve full conversion to **9**. Oxidation of **9** as described above gave the aldehyde **14** and the carboxylic acid **17**.[11]

Aldehyde **14** displayed evidence of instability. During an attempt to use variable-temperature NMR to coalesce rotamer populations, solutions of **14** in DMSO-d_6 heated above 50 °C

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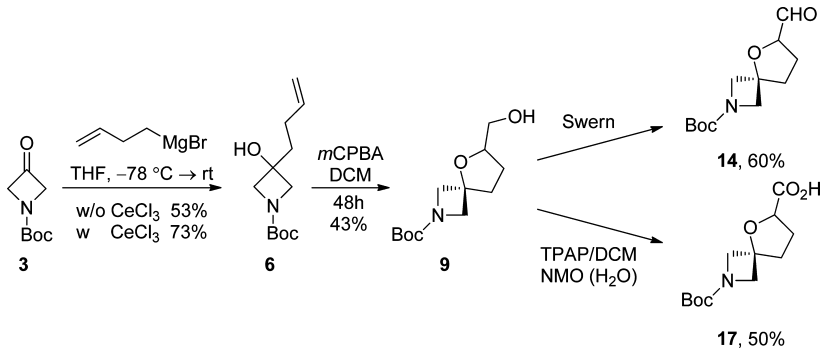
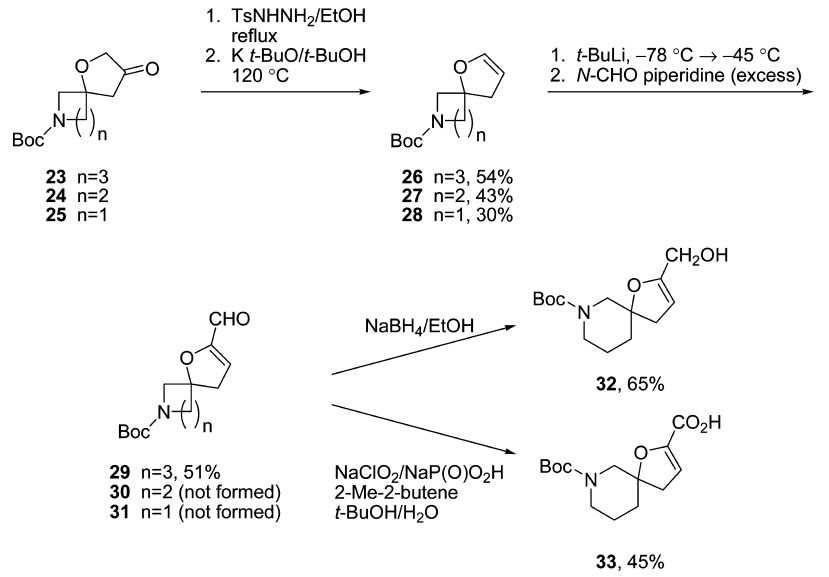
Scheme 6. Racemic Spiro-THF Scaffolds Derived from *N*-Boc-3-azetidinone 3



Scheme 7. Synthesis of Spiro-DHF Scaffolds from *N*-Boc-Protected Spirocyclic 3-Furanones



rapidly darkened with loss of recognizable spectral signals. Further studies showed that while **14** could be reproducibly generated and isolated, storage, even at 0 °C, led to changes in the ^{1}H NMR spectrum that suggested decomposition. Aldehyde **14** should, when prepared, be used without delay. Alcohol **9** and acid **17** had no corresponding liability.

Spirocyclic Dihydrofuran (DHF) Scaffolds Derived from *N*-Boc-Protected Cyclic 2-Aminoketones. The synthetic plan for spiro-DHF containing scaffolds is shown in Scheme 7. The sequence began with the *N*-Boc protected spirocyclic 3-furanones **23**−**25** which were prepared from *N*-Boc protected cyclic 2-aminoketones **1**−**3** as previously reported by this laboratory.[12] The 3-furanones were converted to their corresponding tosylhydrazones (not shown) which were obtained as mixtures of geometric isomers. These were treated with base to give the enol ethers **26**−**28**, which were isolated in the indicated overall yields.[13] Our plan was to lithiate **26**−**28** at the enol ether α position using the method of Paquette, which was the most closely related precedent, and formylate them to afford the derived aldehydes.[14,15] Reduction or oxidation[16] would provide the alcohols or acids, respectively.

Enol ether **26** was used as a model for optimizing the *t*-BuLi lithiation required to complete the synthesis. Deuterium incorporation was measured by quenching the carbanion with CD_3OD and examination of the relative integration of the enol ether signals in the ^{1}H NMR spectrum. In particular, the signal of the α proton at δ 6.24 ($CDCl_3$) was diagnostic. We developed conditions that gave both 100% deuterium incorporation and high mass recovery (90%). Application of these conditions to formylation of **26** with DMF gave aldehyde **29**, although switching to *N*-formylpiperidine improved the yield of the reaction. Reduction of **29** afforded alcohol **32** whereas oxidation afforded acid **33**. Further optimization of this sequence was not pursued.

Turning our attention to enol ethers **27** and **28**, neither afforded significant amounts of **30** or **31**. The reasons for the behavior of these last two substrates were not systematically investigated. However, an indicator of unusual reactivity was observed during the lithiation of **28.** A small amount of a compound identified by ^{1}H and ^{13}C NMR spectroscopy as **34** (Figure 3) was isolated, suggesting that lithiated **28** is exceptionally reactive. This reactivity could cause unproductive processes to occur such as this unexpected Boc transfer.

■ CONCLUSIONS

We have successfully synthesized a series of 17 new spirocyclic scaffolds derived from three *N*-Boc protected cyclic 2-aminoketones. These scaffolds can be prepared in sufficient quantities for further elaboration. This constitutes a method of constructing building blocks for exploring chemical space incrementally in three dimensions. In particular the fully saturated THF containing scaffolds could be obtained in

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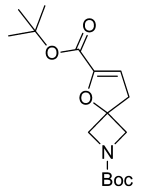

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Figure 3. Byproduct from lithiation/formylation reaction of **28**.

amounts that are suitable for diversification using parallel synthesis. Syntheses of compound libraries derived from some of these core scaffolds have been completed within our laboratory and will be the subject of a separate report.

EXPERIMENTAL SECTION

General Methods. All air- and moisture-sensitive reactions were carried out in flame- or oven-dried glassware under argon atmosphere using standard gastight syringes, cannula, and septa. Stirring was achieved with oven-dried magnetic stir bars. *m*-CPBA was purchased as a 70−75% by weight product. CH_2Cl_2 was purified by passage through a purification system employing activated Al_2O_3. Flash column chromatography was performed with SiO_2 from Sorbent Technology (30930M-25, Silica Gel 60A, 40−63 μm) or by using an automated chromatography instrument with an appropriately sized column. Thin layer chromatography was performed on silica gel 60F254 plates (EM-5717, Merck). Non-UV active compounds were visualized on TLC using $KMnO_4$ stain. ^1H and ^{13}C NMR spectra were recorded on instruments operating at 400 or 500 MHz and 100 or 125 MHz respectively. High-resolution mass spectrometry (HRMS) spectra were obtained on an ESI-TOF mass spectrometer. The analytical method utilized a Waters Aquity BEH C18 column (2.1 × 50 mm, 1.7 μm) eluting with a linear gradient of 95% water (modified to pH 9.8 through addition of NH_4OH) to 100% CH_3CN at 0.6 mL/min flow rate where purity was determined using UV peak area at 214 nm. Melting points were determined using an automated apparatus with digital imaging capability.

3-Butenylmagnesium Bromide. 3-Butenylmagnesium bromide was prepared by the reported procedure.[4] A 100 mL round-bottom flask was fitted with a reflux condenser and dropping funnel with pressure equalizing side arm atop the condenser. The flask was charged with Mg powder (0.293 g, 12.1 mmol) which was activated by adding 1−2 mol % of iodine. After 5 min, THF (15 mL) was added. A solution of 4-bromobutene (1.02 mL, 10 mmol) in THF (4 mL) was added using a dropping funnel. Addition was carried out at a rate sufficient to maintain a gentle reflux. After complete addition the mixture was heated to reflux for 1 h. The solution was cooled to rt and used for further reactions.

Procedure for the Preparation of Alcohols 4 and 5. A suspension of anhydrous powdered $CeCl_3$ (2.56 g, 10.34 mmol) in THF (30 mL) was stirred at rt under argon for 18 h giving a thick, finely divided white suspension. The mixture was cooled to 0 °C, and a solution of 3-butenylmagnesium bromide (10.34 mmol) in THF was added dropwise via canula. The resulting suspension was stirred at this temperature for 2 h. A solution of the ketone (**1**) or (**2**) (5.17 mmol) in THF (10.0 mL) was added dropwise by syringe, and the mixture was stirred at 0 °C for 1 h and then slowly warmed to rt. After 1 h at rt, the mixture was quenched with 5% aq AcOH (10 mL). The organic layer was separated, and the aq layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with water (1 × 10 mL), satd aq $NaHCO_3$ (1 × 10 mL), and brine (1 × 10 mL) and then dried over anhyd Na_2SO_4. Filtration of the mixture followed by evaporation of the solvent gave the crude product which was purified by flash column chromatography using 20%-40% EtOAc/hexanes as eluent to give the desired compound.

***tert*-Butyl 3-(but-3-en-1-yl)-3-hydroxypiperidine-1-carboxylate (4):** 0.90 g, 67%, colorless oil; ^1H NMR ($CDCl_3$, 500 MHz) δ 5.85 (ddt, J = 16.8, 10.1, 6.5 Hz, 1H), 5.06 (dq, J = 17.1, 1.7 Hz, 1H), 4.97 (dq, J = 10.3, 1.4 Hz, 1H), 3.86−3.43 (m, 2H), 2.99 (br s, 2H), 2.22−2.17 (m, 2H), 1.83−1.67 (m, 3H), 1.59−1.53 (m, 3H), 1.46 (s, 9H); ^{13}C NMR (DMSO, 125 MHz, 85 °C) δ 154.8, 139.9, 114.2, 78.8, 68.9, 53.8, 44.1, 37.9, 36.3, 28.7, 27.2, 21.9; IR (neat) 3405, 2977, 1671, 1407 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $(M + H)^+$ $(C_{14}H_{26}NO_3)^+$ 256.1913, found 256.1892.

***tert*-Butyl 3-(but-3-en-1-yl)-3-hydroxypyrrolidine-1-carboxylate (5):** 1.11 g, 90%, colorless oil, mixture of rotamers; ^1H NMR ($CDCl_3$, 500 MHz) δ 5.87 (ddt, J = 16.9, 10.2, 6.6 Hz, 1H), 5.08 (dq, J = 17.1, 1.7 Hz, 1H), 5.00 (dq, J = 10.2, 1.4 Hz, 1H), 3.57−3.45 (m, 2H), 3.43−3.34 (m, 1H), 3.24 (dd, J = 21.5, 11.6 Hz, 1H), 2.23 (p, J = 8.0 Hz, 2H), 1.91−1.87 (m, 1H), 1.75 (ddt, J = 16.8, 11.9, 7.4 Hz, 3H), 1.46 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 154.7, 154.6, 138.39, 138.37, 115.2, 115.1, 79.9, 79.3, 79.1, 58.1, 57.8, 44.7, 44.2, 38.1, 37.9, 37.5, 28.9, 28.8, 28.5; IR (neat) 3406, 2979, 1671, 1407 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $(M + H)^+$ $(C_{13}H_{24}NO_3)^+$ 242.1756, found 242.1746.

***tert*-Butyl 3-(But-3-en-1-yl)-3-hydroxyazetidine-1-carboxylate (6).** A suspension of anhydrous powdered $CeCl_3$ (0.493 g, 2.0 mmol) in THF (5.0 mL) was stirred for 18 h. The resulting white suspension was cooled to −78 °C, and a THF solution of 3-butenylmagnesium bromide (0.203 mL, 2.0 mmol) was added dropwise. The resulting suspension was stirred for an additional 2 h at −78 °C. A solution of **3** (0.171 g, 1.0 mmol) in THF (1.0 mL) was added dropwise at −78 °C, and the mixture was stirred for 1 h at −78 °C. The reaction was allowed to warm slowly to rt with stirring over a period of 16 h. The mixture was quenched with 5% aq AcOH (5 mL). The organic layer was separated, and the aq layers were extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with H_2O, satd aq $NaHCO_3$, and brine and then dried over anhyd Na_2SO_4. Filtration of the mixture and evaporation of the solvent provided a pale yellow solid that was purified by silica gel column chromatography (40% EtOAc/hexanes) to give alcohol **6** as a colorless oil that crystallizes on standing (0.166 g, 0.730 mmol, 73%): mp = 71.5−74.0 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.95−5.82 (m, 1H), 5.12 (dq, J = 17.1, 1.7 Hz, 1H), 5.05 (dq, J = 10.1, 1.4 Hz, 1H), 3.90 (br d, 1/2 AB, J = 9.9 Hz, 2H), 3.82 (br d, 1/2 AB, J = 9.8 Hz, 2H), 2.22 (br dq, J_q = 9.4 Hz, J_d = 3.0 Hz, 2H), 2.25−2.19 (m, 2H), 2.01 (br s, 1H), 1.93−1.85 (m, 2H), 1.47 (s, 9H); ^{13}C NMR (DMSO-d_6, 100 MHz, 85 °C) δ 156.4, 139.1, 114.8, 78.8, 69.5, 62.5, 38.4, 28.6, 27.8; IR (neat) 3405, 2977, 1671, 1407 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $(M + H)^+$ $(C_{12}H_{22}NO_3)^+$ 228.1600, found 228.1593.

Using the above procedure but with omission of $CeCl_3$ gave alcohol **6** in 53% yield.

General Procedure for the Preparation of Spiro Alcohols 8, 10a, and 10b. To a solution of alcohol **4** or **5** (4.31 mmol) in CH_2Cl_2 (20 mL) at rt was added *m*-CPBA (1.59 g, 70 wt %, 6.45 mmol) in one portion. The resulting solution was stirred for 22 h during which time a white precipitate formed. Aliquots were withdrawn and evaporated in vacuo for ^1H NMR spectroscopy to confirm consumption of the olefin (diagnostic olefin signals as reported above). Additional charges of *m*-CPBA were added if required. The mixture was diluted with CH_2Cl_2 (20 mL), and satd aq $NaHCO_3$ (10 mL) was added. The organic layer was removed, and the aq layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phase was washed with brine and then dried over anhyd Na_2SO_4. Filtration of the mixture followed by evaporation of the solvent gave a viscous oil which was purified by flash chromatography using 50−80% EtOAc/hexanes as eluent.

***tert*-Butyl 2-(Hydroxymethyl)-1-oxa-7-azaspiro[4.4]nonane-7-carboxylate (8).** Using the above procedure with **5** as starting material, silica gel chromatography with 80% EtOAc/hexanes as eluent gave 0.95 g (83%) of an inseparable mixture of the two diastereomers (**8**).

***tert*-Butyl 2-(Hydroxymethyl)-1-oxa-7-azaspiro[4.5]decane-7-carboxylate (10a).** Using the above procedure, with (**4**) as starting material, the crude product was chromatographed on silica gel (60% EtOAc/hexanes) to give (**10a**) (0.39 g, 35%, the more retained isomer, pale yellow oil, mixture of rotamers); ^1H NMR ($CDCl_3$, 500 MHz) δ 4.15 (br s, 1H), 3.70−3.66 (m, 1H), 3.53−3.35 (m, 3H),

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3.23−3.08 (m, 2H), 2.01 (br s, 1H), 1.88−1.62 (m, 7H), 1.46 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 154.8, 81.2, 79.4, 78.5, 65.1, 52.0, 51.1, 44.3, 43.3, 36.7, 33.7, 28.4, 26.8, 23.2; IR (neat) 3444, 2933, 1688, 1670 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $(M + H)^+$ $(C_{14}H_{26}NO_4)^+$ 272.1862, found 272.1851.

***tert*-Butyl 2-(Hydroxymethyl)-1-oxa-7-azaspiro[4.5]decane-7-carboxylate (10b).** Using the above procedure, with **4** as starting material, the crude product was chromatographed on silica gel (60% EtOAc/hexanes) to give **10b** (0.43g, 37%, the less retained isomer, pale yellow oil): ^{1}H NMR (CD_3OD, 400 MHz) δ 4.08 (td, J = 7.3, 4.1 Hz, 1H), 3.73−3.40 (m, 4H), 3.29−3.01 (m, 2H), 2.13−1.60 (m, 7H) 1.48 (s, 10H); ^{13}C NMR (DMSO-d_6, 125 MHz, 85 °C) δ 154.8, 80.8, 80.1, 79.0, 64.8, 53.4, 43.9, 36.4, 34.2, 28.7, 27.8, 23.1; IR (neat) 3407, 2934, 1691, 1670, 1424 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $(M + H)^+$ $(C_{14}H_{26}NO_4)^+$ 272.1862, found 272.1850.

***tert*-Butyl 6-(Hydroxymethyl)-5-oxa-2-azaspiro[3.4]octane-2-carboxylate (9).** *m*-CPBA (1.35 g, 70 wt %, 5.48 mmol) was added in one portion to a solution of **6** (0.5 g, 2.20 mmol) in CH_2Cl_2 (25 mL). The resulting solution was stirred for 48 h during which time a white precipitate formed. The mixture was diluted with CH_2Cl_2 (10 mL), and satd aq $NaHCO_3$ (10 mL) was added. The organic layer was removed, and the aq layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine and then dried over anhyd Na_2SO_4. Filtration of the mixture followed by evaporation of the solvent in vacuo gave a viscous oil that was purified by flash chromatography (10−45% EtOAc/hexanes) to give **9** (0.23 g, 0.945 mmol, 43%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.15 (ddd, J = 4.8, 3.5, 1.7 Hz, 1H), 4.02 (dd, J = 17.6, 1.0 Hz, 2H), 3.91−3.86 (m, 2H), 3.71 (dd, J = 11.7, 3.3 Hz, 1H), 3.50 (dd, J = 11.7, 5.8 Hz, 1H), 2.19−2.08 (m, 2H), 2.01−1.94 (m, 1H), 1.76 (dd, J = 12.5, 8.0 Hz, 1H), 1.46 (s, 9H); ^{13}C NMR (DMSO-d_6, 100 MHz, 85 °C) δ 156.2, 80.7, 78.9, 78.6, 64.3, 62.8, 62.2, 35.6, 28.6, 27.2; IR (neat) 3427, 2974, 1678, 1392 cm^{-1}; HRMS (ESI-TOF) m/z calcd for (2 M + H)$^+$ $(C_{24}H_{43}N_2O_8)^+$ 487.3019, found 487.3028 (base peak); m/z calcd for $(M + H)^+$ $(C_{12}H_{22}NO_4)^+$ 245.1549, found 245.1575.

***tert*-Butyl 2-(((4-Methoxybenzoyl)oxy)methyl)-1-oxa-7-azaspiro[4.5]decane-7-carboxylate (18a).** *p*-Methoxybenzoyl chloride (0.23 g, 1.38 mmol) was added to a solution of alcohol **10a** (0.187 g, 0.689 mmol) in dry py (2 mL) at rt under Ar. After 19 h, py was evaporated in vacuo. The residue was diluted with DCM (5 mL) and water (5 mL). The organic layer was recovered, and the aq layer was extracted with DCM (2 × 5 mL). The combined organic extracts were washed with 0.5 N aq HCl (2 × 10 mL), water (1 × 10 mL), and brine (1 × 10 mL) and then dried over anhyd Na_2SO_4. After filtration of the mixture, all volatiles were evaporated in vacuo and the crude product was purified by silica gel column chromatography using 20−40% EtOAc/hexanes as eluent to give 0.24 g (86%) of pure compound (**18a**) (colorless oil, mixture of two rotamers): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95−7.91 (m, 2H), 6.86−6.83 (m, 2H), 4.32−4.17 (m, 3H), 3.79 (s, 3H), 3.60−3.35 (m, 2H), 3.03 (t, J = 14.2 Hz, 2H), 2.08 (br s, 1H), 1.90−1.77 (m, 2H), 1.73−1.54 (m, 5H), 1.38 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 163.4, 155.1, 131.7, 122.5, 113.6, 81.5, 79.4, 76.1, 66.8, 55.4, 36.8, 33.1, 28.5, 27.8, 23.4; IR (neat) 2976, 1712, 1688, 1605, 1251, 1163 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $(M + H)^+$ $(C_{22}H_{32}NO_6)^+$ 406.2229, found 406.2247.

2-(((4-Methoxybenzoyl)oxy)methyl)-1-oxa-7-azaspiro[4.5]-decan-7-ium Chloride (19a). TFA (0.31 mL, 4.05 mmol) was added to a solution of **18a** (69 mg, 0.17 mmol) in DCM (2 mL) at rt. The reaction mixture slowly became light yellow and was stirred at rt for 1 h. All volatiles were removed in vacuo. Saturated aq $NaHCO_3$ (4 mL) was added and the solution was stirred at rt for 2 h. The reaction mixture was extracted with DCM (3 × 3 mL). The organic extracts were evaporated to give the free amine which was suspended in deionized water (1 mL) and acidified with 0.1 N aq HCl to pH ∼2 (by pH meter). The mixture was stirred further for 30 min until homogeneous and then lyophilized over a period of 48 h to give a clear viscous oil. The oil was layered with isopropyl acetate and heated to just below reflux, then MeOH was slowly added dropwise until homogeneous. The solution was allowed to stand in a loosely capped vial in the hood for 3 d, affording X-ray quality crystals of **19a**: HRMS (ESI-TOF) m/z calcd for $(M - HCl + H)^+$ $(C_{17}H_{24}NO_4)^+$ 306.1705, found 306.1720.

***tert*-Butyl 2-(((4-Methoxybenzoyl)oxy)methyl)-1-oxa-7-azaspiro[4.4]nonane-7-carboxylate (21a) and (21b).** *p*-Methoxybenzoyl chloride (4.51 g, 26.4 mmol) was added to a solution of alcohols **8** (3.40 g, 13.21 mmol) in dry py (13 mL) at rt under Ar. After 20 h, py was evaporated in vacuo. The residue was diluted with DCM (50 mL) and water (50 mL). The organic layer was recovered, and the aq layer was extracted with DCM (2 × 20 mL). The combined organic extracts were washed with 0.5 N aq HCl (2 × 50 mL), water (1 × 50 mL), and brine (1 × 50 mL) and then dried over anhyd Na_2SO_4. After filtration of the mixture, all volatiles were evaporated in vacuo, and the crude product **20** was purified by silica gel column chromatography using 30% EtOAc/hexanes as eluent to give a total of 3.72 g (72%) of pure diastereomers **21a** and **21b** (1:1 ratio).

21a: 1.86 g, 36%, the less retained isomer, colorless oil, mixture of two rotamers; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.95−7.92 (m, 2H), 6.87−6.84 (m, 2H), 4.30−4.21 (m, 3H), 3.79 (s, 3H), 3.43−3.33 (m, 3H), 3.18 (t, J = 11.2 Hz, 1H), 2.04 (dt, J = 13.4, 6.6 Hz, 1H), 2.00−1.88 (m, 3H), 1.88−1.72 (m, 2H), 1.38 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.2, 163.43, 163.41, 154.6, 154.5, 131.7, 122.44, 122.40, 113.6, 88.8, 88.0, 79.22, 79.18, 76.6, 66.4, 56.2, 55.7, 55.4, 45.1, 44.7, 37.4, 36.8, 33.8, 33.5, 28.5, 28.32, 28.30; IR (neat) 2972, 1712, 1693, 1606, 1403 cm^{-1}; HRMS (ESI-TOF) m/z calcd for (2 M + H)$^+$ $(C_{42}H_{59}N_2O_{12})^+$ 783.4068, found 783.4072 (base peak); m/z calcd for $(M + H)^+$ $(C_{21}H_{30}NO_6)^+$ 392.2073, found 392.2071.

21b: 1.86 g, 36%, the more retained isomer, colorless oil, mixture of two rotamers; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.95−7.93 (m, 2H), 6.87−6.84 (m, 2H), 4.31−4.21 (m, 3H), 3.79 (s, 3H), 3.42−3.22 (m, 4H), 2.08−1.95 (m, 3H), 1.87−1.80 (m, 2H), 1.73 (tt, J = 12.3, 8.3 Hz, 1H), 1.38 (s, 4.0 H), 1.37 (s, 5.0 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.26, 166.24, 163.4, 154.49, 154.47, 131.72, 131.71, 122.40, 122.38, 113.65, 113.64, 88.8, 88.0, 79.24, 79.18, 76.7, 66.40, 66.38, 56.6, 56.2, 55.4, 45.0, 44.6, 36.8, 36.2, 34.1, 33.9, 28.5, 28.3, 28.2; IR (neat) 2971, 1714, 1694, 1606, 1404 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $(M + H)^+$ $(C_{21}H_{30}NO_6)^+$ 392.2073, found 392.2074.

***tert*-Butyl 2-(Hydroxymethyl)-1-oxa-7-azaspiro[4.4]nonane-7-carboxylates (11a) and (11b).** A solution of NaOMe in MeOH (0.83 mL, 25 wt %, 3.83 mmol) was added to a solution of *p*-methoxybenzoate (**21a**) or (**21b**) (0.75 g, 1.92 mmol) in anhyd MeOH (10 mL) at rt. The reaction mixture was stirred at rt for 16 h. The solvent was evaporated in vacuo and the residue was treated with 5% aq acetic acid (10 mL). The reaction mixture was extracted with DCM (3 × 10 mL). The combined organic extracts were washed with satd aq $NaHCO_3$ solution (2 × 10 mL) and brine (1 × 20 mL) and then dried over anhyd Na_2SO_4. After filtration of the mixture, all volatiles were removed and the crude product was purified by column chromatography using 80% EtOAc/hexanes as eluent.

11a: 0.47 g, 95%, colorless oil, mixture of two rotamers; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.06−4.02 (m, 1H), 3.64 (dd, J = 11.5, 3.3 Hz, 1H), 3.46−3.33 (m, 4H), 3.16 (t, J = 10.9 Hz, 1H), 1.94−1.76 (m, 6H), 1.39 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 154.6, 154.5, 88.7, 87.9, 79.30, 79.27, 79.23, 79.0, 65.1, 64.9, 56.2, 55.6, 45.1, 44.7, 37.3, 36.9, 33.9, 33.7, 28.5, 27.31, 27.26; IR (neat) 3432, 2973, 1692, 1673, 1401 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $(M + H - Boc)^+$ $(C_8H_{16}NO_2)^+$ 158.1181, found 158.1176.

11b: 0.46 g, 93%, colorless oil, mixture of two rotamers; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.05 (dddd, J = 7.5, 6.5, 5.5, 3.3 Hz, 1H), 3.65−3.61 (m, 1H), 3.46−3.21 (m, 5H), 1.98−1.89 (m, 4H), 1.78−1.69 (m, 2H), 1.39 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 154.6, 154.5, 88.7, 87.9, 79.38, 79.31, 79.26, 79.16, 77.2, 65.1, 65.0, 56.6, 56.2, 45.1, 44.6, 36.7, 36.1, 34.1, 33.9, 28.5, 27.31, 27.26; IR (neat) 2972, 1692, 1673, 1402 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $(M + H - Boc)^+$ $(C_8H_{16}NO_2)^+$ 158.1181, found 158.1171.

***tert*-Butyl 2-Formyl-1-oxa-7-azaspiro[4.5]decane-7-carboxylate (12a).** A solution of oxalyl chloride (0.017 mL, 0.19 mmol) in CH_2Cl_2 (2.0 mL) was cooled to −78 °C, and a solution of DMSO (0.027 mL, 0.38 mmol) in CH_2Cl_2 (0.5 mL) was added dropwise. The resulting solution was stirred for 15 min at this temperature. A solution of the alcohol **10a** or **10b** (0.128 mmol) in CH_2Cl_2 (1.0 mL) was

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added dropwise and the mixture was stirred for 1 h at −78 °C. Triethylamine (0.089 mL, 0.64 mmol) was then added dropwise, and the mixture was allowed to warm slowly to rt over a period of 1 h. After 1 h, the reaction was diluted with CH_2Cl_2 (2 mL) and water (5 mL). The organic phase was removed, and the aq layer was extracted with CH_2Cl_2 (3 × 2 mL). The combined organic layers were washed with H_2O (1 × 5 mL) and brine (1 × 5 mL) and dried over anhyd Na_2SO_4. After filtration of the mixture the solvent was evaporated in vacuo and the crude product was purified by column chromatography using 60−80% EtOAc/hexanes as eluent. **12a**: 0.028 g, 81%; colorless oil, mixture of two rotamers; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.60 (d, J = 1.5 Hz, 1H), 4.30 (br s, 1H), 3.46−3.36 (m, 2H), 3.16−3.07 (m, 2H), 2.25−2.11 (m, 1H), 2.03 (ddt, J = 13.5, 8.5, 5.0 Hz, 1H), 1.87−1.80 (m, 1H), 1.73 (dddd, J = 12.5, 8.5, 6.8, 4.1 Hz, 2H), 1.66−1.57 (m, 2H), 1.49−1.43 (m, 1H), 1.38 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 202.7, 154.9, 82.8, 82.6, 79.6, 51.9, 51.0, 44.2, 43.2, 36.3, 33.0, 28.4, 27.1, 23.2; IR (neat) 2974, 1733, 1686, 1420 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $(M + H)^+$ $(C_{14}H_{24}NO_4)^+$ 270.1705, found 270.1705.

***tert*-Butyl 2-Formyl-1-oxa-7-azaspiro[4.4]nonane-7-carboxylate (13a) and (13b).** Following the above procedure for preparation of **12a** and using either **11a** or **11b** as starting material, aldehydes **13a** or **13b** was obtained.

13a: 0.027 g, 82%, colorless oil, mixture of two rotamers; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.68 (d, J = 1.6 Hz, 1H), 4.37 (q, J = 7.3 Hz, 1H), 3.55−3.44 (m, 3H), 3.28 (dd, J = 11.5, 4.2 Hz, 1H), 2.29−2.20 (m, 1H), 2.15−1.99 (m, 3H), 1.95−1.86 (m, 2H), 1.46 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 202.3, 202.1, 154.5, 154.4, 90.2, 89.4, 82.8, 82.7, 79.4, 56.0, 55.5, 45.1, 44.6, 36.9, 36.3, 33.3, 32.9, 28.5, 27.62, 27.58; IR (neat) 2974, 1733, 1691, 1403 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $(2\ M + H)^+$ $(C_{26}H_{43}N_2O_8)^+$ 511.3019, found 511.3011 (base peak); m/z calcd for $(M + H)^+$ $(C_{13}H_{22}NO_4)^+$ 256.1549, found 256.1562.

13b. 0.030 g, 87% colorless oil, mixture of two rotamers; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.69−9.67 (m, 1H), 4.41−4.33 (m, 1H), 3.51 (ddt, J = 22.7, 8.8, 5.2 Hz, 3H), 3.35 (dd, J = 19.8, 11.6 Hz, 1H), 2.29−2.23 (m, 1H), 2.15−2.03 (m, 2H), 1.96 (dt, J = 14.5, 7.2 Hz, 2H), 1.91−1.81 (m, 1H), 1.47 (s, 9H); ^{13}C NMR ($CDCl_3$,125 MHz) δ 202.5, 202.2, 154.4, 90.3, 89.5, 82.9, 82.8, 79.5, 79.4, 56.1, 55.8, 45.1, 44.6, 36.7, 36.1, 33.3, 28.5, 27.9, 27.6; IR (neat) 2974, 1733, 1692, 1403 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $(M + H)^+$ $(C_{13}H_{22}NO_4)^+$ 256.1549, found 256.1561.

***tert*-Butyl 6-Formyl-5-oxa-2-azaspiro[3.4]octane-2-carboxylate (14).** A solution of oxalyl chloride (0.185 mL, 2.14 mmol) in CH_2Cl_2 (5.0 mL) was cooled to −78 °C, and a solution of DMSO (0.304 mL, 4.27 mmol) in CH_2Cl_2 (2.0 mL) was added dropwise. The resulting solution was stirred for 15 min at this temperature. A solution of **9** (0.104 g, 0.427 mmol) in CH_2Cl_2 (2.5 mL) was then added dropwise and the mixture was stirred for 1 h at −78 °C. Triethylamine (0.894 mL, 6.41 mmol) was added and the mixture was allowed to warm slowly to rt. After 30 min the reaction was diluted with CH_2Cl_2 (10 mL) and satd aq $NaHCO_3$ (10 mL). The organic phase was separated and the aq layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with H_2O (10 mL) and brine (10 mL) and then dried over anhyd Na_2SO_4. Filtration of the mixture and evaporation of the solvent, followed by flash chromatography (10−50% EtOAc/Hex), gave the aldehyde (**14**) (0.06 g, 0.25 mmol, 58%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.67 (d, J = 1.6 Hz, 1H), 4.41 (ddd, J = 7.9, 6.1, 1.6 Hz, 1H), 4.13 (ddd, J = 11.8, 9.2, 1.1 Hz, 2H), 3.91 (ddd, J = 9.2, 5.6, 1.1 Hz, 2H), 2.28−1.99 (m, 4H), 1.46 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 201.3, 156.4, 83.3, 79.84, 79.81, 77.2, 61.3 (broad peak), 35.2, 28.4, 26.8; IR (neat) 2972, 2876, 1730, 1698, 1399 cm^{-1}; HRMS (ESI-TOF) m/z calcd for negative ion $(M - H)^-$ $(C_{12}H_{18}NO_4)^-$ 240.1236, found 240.1214.

7-(*tert*-Butoxycarbonyl)-1-oxa-7-azaspiro[4.5]decane-2-carboxylic Acid (15a) and (15b). NMO·H_2O (0.446 g, 3.3 mmol) was added at rt to the solution of alcohol **10a** or **10b** (0.33 mmol) in CH_3CN (5 mL). TPAP (11.6 mg, 0.033 mmol) was added, and the reaction mixture was further stirred at rt for 16 h in a closed vessel. Water (2 mL) was added, and the reaction mixture was acidified with satd aq sodium hydrogen sulfate to pH ∼3. DCM (10 mL) was added and the organic phase was separated. The aq phase was extracted with DCM (3 × 3 mL). The combined organic extracts were washed with water (1 × 10 mL), brine (1 × 10 mL) and dried over anhyd Na_2SO_4. The mixture was filtered and the solvent was evaporated in vacuo. The crude product was purified using 5%-20% MeOH/DCM as eluent.

15a: 0.050 g, 53%, white solid; mp 94.0−96.0 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.24 (s, 1H), 4.58 (dd, J = 8.3, 4.2 Hz, 1H), 3.71−3.41 (m, 2H), 3.24−3.07 (m, 2H), 2.43 (br s, 1H), 2.23 (br s, 1H), 1.94 (ddd, J = 12.3, 8.1, 4.3 Hz, 1H), 1.89−1.74 (m, 3H), 1.66 (dt, J = 12.2, 8.7 Hz, 1H), 1.54−1.46 (m, 10H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 176.1, 155.1, 154.7, 83.7, 79.8, 76.4, 51.8, 50.8, 44.2, 43.2, 36.3, 32.7, 32.5, 29.5, 28.4, 23.4, 23.22; IR (neat) 2935, 1749, 1688, 1647, 1423 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $(M + H - Boc)^+$ $(C_9H_{16}NO_3)^+$ 186.1130, found 186.1126.

15b: 0.059 g, 63%, colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.51 (t, J = 7.2 Hz, 1H), 4.07 (d, J = 13.0 Hz, 2H), 2.94−2.71 (m, 2H), 2.41 (dq, J = 13.5, 7.0 Hz, 1H), 2.25 (dq, J = 12.8, 7.6 Hz, 1H), 1.94−1.79 (m, 3H), 1.74 (dt, J = 12.8, 7.8 Hz, 1H), 1.63−1.54 (m, 2H), 1.50 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.5, 157.8, 83.8, 80.9, 77.9, 53.4, 45.7, 35.9, 34.5, 30.5, 28.4, 22.5; IR (neat) 2936, 1751, 1689, 1659, 1423 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $(M + H - Boc)^+$ $(C_9H_{16}NO_3)^+$ 186.1130, found 186.1136.

7-(*tert*-Butoxycarbonyl)-1-oxa-7-azaspiro[4.4]nonane-2-carboxylic acid (16a) and (16b). Using the above procedure for the preparation of acids **15a**/**15b** with **11a** or **11b** as starting materials the acids **16a** and **16b** were obtained.

16a: 0.049 g, 55%, colorless oil, mixture of two rotamers; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.51 (br s, 1H), 4.57 (dd, J = 8.6, 5.6 Hz, 1H), 3.55−3.43 (m, 3H), 3.28 (t, J = 11.2 Hz, 1H), 2.40 (dq, J = 13.0, 7.8 Hz, 1H), 2.31−2.13 (m, 2H), 2.10−1.81 (m, 3H), 1.45 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 176.5, 176.3, 154.7, 154.6, 90.6, 89.9, 79.69, 79.64, 77.2 76.6, 76.4, 56.1, 55.5, 45.1, 44.6, 36.6, 36.1, 33.2, 32.9, 30.3, 30.2, 28.5; IR (neat) 2975, 1738, 1690, 1666, 1640, 1412 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $(2\ M + H)^+$ $(C_{26}H_{43}N_2O_{10})^+$ 543.2918, found 543.2925 (base peak); m/z calcd for $(M + H)^+$ $(C_{13}H_{22}NO_5)^+$ 272.1498, found 272.1509.

16b: 0.047 g, 53%, colorless oil, mixture of two rotamers; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.26 (br s, 1H), 4.57 (dt, J = 9.0, 4.4 Hz, 1H), 3.67−3.35 (m, 4H), 2.46−2.36 (m, 1H), 2.26−2.18 (m, 1H), 2.10−2.01 (m, 2H), 1.97−1.90 (m, 1H), 1.82 (tt, J = 12.8, 8.5 Hz, 1H), 1.46 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 175.8, 175.3, 154.8, 154.6, 90.8, 89.9, 79.8, 79.7, 76.5, 55.9, 55.5, 45.0, 44.5, 36.8, 36.2, 33.1, 30.2, 28.5; IR (neat) 2974, 1739, 1691, 1667, 1645, 1411 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $(M + H)^+$ $(C_{13}H_{22}NO_5)^+$ 272.1498, found 272.1509.

2-(*tert*-Butoxycarbonyl)-5-oxa-2-azaspiro[3.4]octane-6-carboxylic Acid (17). A 25 mL round-bottom flask was charged with NMO·0.21H_2O (0.481 g, 4.11 mmol), water (0.037 mL, 2.0 mmol), and alcohol **9** (0.100 g, 0.41 mmol) as a solution in CH_2Cl_2 (2.0 mL). Tetrapropylammonium perruthenate (14.5 mg, 0.041 mmol, 10 mol %) was added to this mixture at rt. The mixture was stirred for 30 min during which time the color changed from green to yellow. The reaction was quenched with 5% aq acetic acid (5 mL). The organic layer was separated and the aq layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine and dried over anhyd Na_2SO_4. After filtration of the mixture, evaporation of the solvent gave a viscous oil that was purified by flash chromatography (5%−20% MeOH in DCM) to provide **17** (0.055 g, 0.214 mmol, 52%) as white crystalline solid: mp = 123.5−127.3 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.50 (dd, J = 8.1, 5.3 Hz, 1H), 4.14 (d, J = 9.4 Hz, 1H), 4.03 (d, J = 9.3 Hz, 1H), 3.83 (ddd, J = 9.3, 4.5, 1.1 Hz, 2H), 2.36−2.23 (m, 1H), 2.20−2.00 (m, 3H), 1.37 (s, 9H); ^{13}C NMR (DMSO-d_6, 125 MHz, 85 °C) δ 173.80, 156.4, 80.1, 79.3, 77.5, 62.5, 61.8, 35.0, 29.5, 28.6. IR (neat) 2373, 2924, 1740, 1702, 1428 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $(M + H)^+$ $(C_{12}H_{20}NO_5)^+$ 258.1341, found 258.1346.

1-Oxa-7-azaspiro[4.4]nonan-2-ylmethyl 4-Methoxybenzoate Hydrochloride (22a). TFA (0.31 mL, 4.05 mmol) was

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added to a solution of **21a** (66 mg, 0.17 mmol) in DCM (2 mL) at rt. The reaction mixture slowly became light yellow and was stirred at rt for 1 h. All volatiles were removed in vacuo. Saturated aq $NaHCO_3$ (4 mL) was added, and the solution was stirred at rt for 2 h. The reaction mixture was extracted with DCM (3 × 3 mL). The organic extracts were evaporated to give the free amine which was suspended in deionized water (1 mL) and acidified with 0.1 N aq HCl to pH ~2 (by pH meter). The mixture was stirred further for 30 min until homogeneous and then lyophilized over a period of 48 h to give crystals of **22a**: HRMS (ESI-TOF) m/z calcd for $(M - HCl + H)^+$ $(C_{16}H_{22}NO_4)^+$ 292.1549, found 292.1532.

***tert*-Butyl 1-Oxa-7-azaspiro[4.5]dec-2-ene-7-carboxylate (26).** A solution of **23** (0.559 g, 2.189 mmol) and 4-methylbenzenesulfonohydrazide (0.510 g, 2.740 mmol) in EtOH (5.47 mL) was heated to reflux for 4.5 h. The reaction mixture was cooled and diluted with water and DCM, and the layers were separated. The aq layer was extracted with DCM (×3), and the combined organic layers were dried over anhyd $MgSO_4$, filtered, and concentrated under vacuum. The crude material was chromatographed on silica gel (20–40% EtOAc in hexanes) to afford the tosylhydrazones (0.925 g, 85%) as a white, amorphous solid that appeared by ^1H NMR spectroscopy to be a mixture of the corresponding geometric isomers. This compound was taken to the next step without further characterization.

In a procedure similar to that of Smith,[13] to a solution of the tosylhydrazones derived from **23** (1.056 g, 2.493 mmol) in *tert*-butyl alcohol (12.5 mL) was added potassium *tert*-butoxide (0.582 g, 5.190 mmol). The reaction mixture was heated in a sealed pressure tube at 120 °C for 18 h (CAUTION: evolved nitrogen was vented periodically during the first 4–6 h. Ample head space in the tube was also provided). The reaction mixture was cooled, diluted with water and isopropyl acetate and the layers separated. The aq layer was extracted with isopropyl acetate (×3). The combined organic layers were washed with brine, dried over anhyd $MgSO_4$, filtered and concentrated under vacuum. The crude material was chromatographed on silica gel (0 to 10% EtOAc in hexanes) to give **26** (0.597 g, 63%) as a white solid: mp = 84.0–86.5 °C; ^1H NMR (DMSO-d_6, 500 MHz, 90 °C) δ 6.29 (br s, 1H), 4.85 (d, J = 2.5 Hz, 1H), 3.40 (dd, J = 12.8, 7.4 Hz, 2H), 3.31–3.26 (m, 2H), 2.38 (d, J = 15.2 Hz, 1H), 2.29 (d, J = 15.2 Hz, 1H), 1.81–1.80 (m, 1H), 1.74–1.70 (m, 2H), 1.48–1.47 (m, 1H), 1.43 (s, 9H); ^{13}C NMR (DMSO-d_6, 125 MHz, 90 °C) δ 153.6, 143.6, 97.3, 82.6, 77.9, 50.5, 42.4, 37.2, 34.3, 27.4, 21.2; IR 2935, 1693 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $(M + H - Boc)^+$ $(C_8H_{14}NO)^+$ 140.1075, found 140.1067.

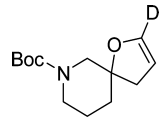
***tert*-Butyl 1-Oxa-7-azaspiro[4.4]non-2-ene-7-carboxylate (27).** Following the above procedure for preparation of **26**, using **24** as starting material (1.611 g, 6.680 mmol) and 4-methylbenzenesulfonohydrazide (1.865 g, 10.02 mmol) as reagent, the mixture of tosylhydrazones (2.240 g, 82%) was obtained as a white, amorphous solid that was used without further characterization.

Following the above procedure, a solution of the tosylhydrazones derived from **24** (0.726 g, 1.772 mmol) in *tert*-butyl alcohol (10 mL) was reacted with potassium *tert*-butoxide (0.414 g, 3.690 mmol) to afford the product **27** (0.206 g, 52%) as a colorless oil: ^1H NMR ($CDCl_3$, 500 MHz) δ 6.19 (s, 1H), 4.83 (dd, J = 5.2, 2.5 Hz, 1H), 3.73–3.36 (m, 3H), 3.23 (dd, J = 11.7, 6.4 Hz, 1H), 2.65–2.60 (m, 1H), 2.54 (d, J = 15.6 Hz, 1H), 2.16–2.12 (m, 1H), 1.85–1.79 (m, 1H), 1.41 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) ~1:1 mixture of rotamers; δ 154.3, 144.1, 98.8, 98.7, 90.8, 90.1, 79.2, 79.1, 57.4, 56.9, 45.1, 44.6, 37.8, 37.2, 36.7, 36.5, 28.4; IR (neat) 2976, 1692 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $(M + H)^+$ $(C_{12}H_{20}NO_3)^+$ 226.1443, found 226.1459.

***tert*-Butyl 5-Oxa-2-azaspiro[3.4]oct-6-ene-2-carboxylate (28).** Following the above procedure for preparation of **26** with **25** as starting material (0.562 g, 2.473 mmol) and 4-methylbenzenesulfonohydrazide (0.691 g, 3.710 mmol) as reagent, the derived tosylhydrazones (0.678 g, 69%) were obtained as a white, amorphous solid.

Following the above procedure, a solution of the tosylhydrazones derived from **25** (0.602 g, 1.523 mmol) in *tert*-butanol (10 mL) were reacted with potassium *tert*-butoxide (0.355 g, 3.170 mmol) to afford the product **28** (0.140 g, 44%) as a white solid: mp = 58.1–60.4 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.24 (dd, J = 5.0, 2.4 Hz, 1H), 4.88 (dd, J = 2.4, 2.4 Hz, 1H), 4.14 (d, J = 10.0 Hz, 2H), 3.91 (d, J = 9.7 Hz, 2H), 2.83 (dd, J = 2.4, 2.4 Hz, 2H), 1.43 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.2, 144.5, 99.1, 80.0, 79.6, 63.7, 39.8, 28.3; IR (neat) 2977, 1700 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $(M + H)^+$ $(C_{11}H_{18}NO_3)^+$ 212.1287, found 212.1292.

***tert*-Butyl 2-Deutero-1-oxa-8-azaspiro[4.5]dec-2-ene-8-carboxylate (35).**



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A −78 °C solution of **26** (0.102 g, 0.428 mmol) in dry THF (3 mL) was treated with *tert*-butyllithium (0.660 mL of a 1.42 M solution in pentane, 0.941 mmol). The reaction mixture was stirred for 20 min, warmed to −45 °C, and stirred for an additional 2 h. The reaction mixture was cooled back to −78 °C, and anhyd methanol-d_4 (1 mL) was added. The mixture was stirred for 10 min then warmed to rt. The reaction mixture was diluted with toluene and concentrated under vacuum. Toluene was again added giving a white suspension that was filtered and concentrated under vacuum to give compound **35** (0.092 mg, 90%) as a white solid. ^1H NMR indicated complete conversion to the deuterated species as evidenced by the absence of the enol ether α proton signal at δ 6.24: ^1H NMR ($CDCl_3$, 400 MHz) δ 4.83 (d, J = 2.3 Hz, 1H), 3.43–3.29 (m, 4H), 2.41 (m, 1H), 2.31 (dd, J = 15.2, 2.3 Hz, 1H), 1.92–1.65 (m, 3H), 1.55–1.40 (m, 10H); HRMS (ESI-TOF) m/z calcd for $(M + H)^+$ $(C_{13}H_{21}DNO_3)^+$ 241.1662, found 241.1680.

***tert*-Butyl 2-Formyl-1-oxa-8-azaspiro[4.5]dec-2-ene-8-carboxylate (29).** To a −78 °C solution of **26** (0.094 g, 0.391 mmol) in THF (2.60 mL) was added *tert*-butyllithium (0.560 mL of a 1.55 M solution in pentane, 0.860 mmol). The reaction mixture was stirred for 20 min, warmed to −45 °C, and then stirred for an additional 2 h. The reaction mixture was then cooled back to −78 °C, and *N*-formylpiperdine (1 mL) was added dropwise over 3–4 min. The reaction mixture was stirred for 20 min, warmed to −45 °C, and then stirred for 18 h. The mixture was slowly warmed to 0 °C in 15 °C increments over 2 h and then stirred at 0 °C for an additional 1 h. The reaction was then quenched with satd aq $NaHCO_3$. The mixture was diluted with water and MTBE, and the layers were separated. The aq layer was extracted with MTBE (×3), and the combined organic layers were washed with water (×2) and brine (×1). The organic layer was dried over anhyd $MgSO_4$, filtered and concentrated under vacuum. The crude material was chromatographed on silica gel (0 to 20% EtOAc in hexanes) to give the product **29** (0.053 g, 51%) as a viscous brown oil and recovered starting material (0.005 g, 5%) as a white solid. Reaction of **26** (0.102 mg), *tert*-butyllithium (0.620 mL of a 1.51 M solution in pentane, 0.934 mmol), and DMF (1 mL) in the same fashion also afforded the product **29** (0.041 mg, 36%) with no recovered starting material: ^1H NMR ($CDCl_3$, 500 MHz, −45 °C), ~1:1 mixture of rotamers; δ 9.39 (s, 0.56 H), 9.36 (s, 0.44H), 6.09 (s, 0.56H), 6.06 (s, 0.44H), 3.95–3.56 (m, 2H), 3.10–2.79 (m, 2H), 2.79–2.51 (m, 2H), 1.85–1.74 (m, 3H), 1.45–1.38 (m, 1H), 1.37 (br s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz, −45 °C) ~1:1 mixture of rotamers; δ 182.4, 154.9, 154.6, 154.5, 154.4, 121.7, 121.2, 85.6, 79.9, 50.8, 49.7, 43.2, 42.1, 38.8, 38.6, 35.1, 34.9, 28.0, 22.2, 21.9; IR (neat) 2976, 1686 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $(M + H)^+$ $(C_{14}H_{22}NO_4)^+$ 268.1549, found 268.1571.

Di-*tert*-butyl 5-Oxa-2-azaspiro[3.4]oct-6-ene-2,6-dicarboxylate (34). Following the above procedure for preparation of **29**, compound **31** (0.103 g, 0.488 mmol) was reacted with *tert*-butyllithium (0.886 mL of a 1.21 M solution in pentane, 1.073 mmol) and *N*-formylpiperdine (1 mL, excess). The byproduct **34** (0.003 mg, 2%) was isolated as a white solid: ^1H NMR ($CDCl_3$, 400 MHz) δ 5.84 (t, J = 3.0 Hz, 1H), 4.25 (dd, J = 9.6, 0.9 Hz, 2H), 3.97 (d, J = 9.6 Hz, 2H), 2.97 (d, J = 3.0 Hz, 2H), 1.46 (s, 9H), 1.25 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 198.0, 156.2, 153.9, 109.4, 81.4,

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80.0, 43.5, 40.2, 29.7, 28.3, 25.9; IR (neat) 2928, 1707, 1608 cm^{-1}. No molecular ion was observed.

***tert*-Butyl 2-(Hydroxymethyl)-1-oxa-8-azaspiro[4.5]dec-2-ene-8-carboxylate (32).** To a solution of **29** (0.030 g, 0.111 mmol) in absolute ethanol (1.11 mL) was added sodium borohydride (0.005 g, 0.133 mmol). The reaction mixture was stirred for 30 min and then diluted with toluene, filtered through a pad of Celite, and concentrated under vacuum. The residue was redissolved in a 1:1 solution of DCM/EtOAc and filtered through a 1 g silica gel SPE that had been pretreated with a solution of 2% triethylamine in hexanes. Further elution was done with EtOAc, affording the pure product **32** (0.019 g, 65%) as a viscous brown oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.82 (br s, 1H), 4.08 (br s, 2H), 3.93−3.06 (br m, 4H), 2.79−2.76 (m, 1H), 2.39−2.35 (m, 2H), 2.05−1.73 (br m, 2H), 1.72−1.70 (m, 1H), 1.58−1.50 (m, 1H), 1.46 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz, −45 °C) ∼2:1 mixture of rotamers; rotamer 1: δ 156.6, 154.5, 97.8, 84.8, 80.0, 57.6, 50.2, 44.6, 38.1, 34.0, 28.1, 22.1; rotamer 2: δ 154.8, 154.3, 95.7; 84.0, 79.8, 58.1, 51.3, 42.4, 38.2, 35.1, 28.2, 22.0; IR: 3426, 2933, 1676 cm^{-1}; HRMS (ESI-TOF) *m*/*z* calcd for $(M + H - Boc)^+$ $(C_9H_{16}NO_2)^+$ 170.1181, found 170.1203.

8-(*tert*-Butoxycarbonyl)-1-oxa-8-azaspiro[4.5]dec-2-ene-2-carboxylic Acid (33). In a manner similar to that of Snider,[16] to a solution of **29** (0.027 mg, 0.099 mmol) and 2-methyl-2-butene (0.238 mL or a 2 M solution in THF, 0.476 mmol) in *tert*-butyl alcohol (0.90 mL) at 0 °C was added a solution of sodium chlorite (0.012 mg of an 80 wt % solid, 0.109 mmol) and monobasic sodium phosphite hydrate (0.015 g, 0.109 mmol) in water (0.10 mL). The reaction mixture was warmed to rt and stirred for 90 min. The mixture was diluted with water and acidified to pH ∼3.00 with 0.1 M aq HCl as determined by pH meter. The mixture was extracted into EtOAc (×3), and the combined organic layers were dried over anhyd $MgSO_4$, filtered, and concentrated under vacuum. The crude material was chromatographed on silica gel (1% AcOH, 30% EtOAc in hexanes) to afford **33** (0.013 g, 45%) as an amorphous white solid: ^{1}H NMR ($CDCl_3$, 500 MHz, 50 °C) δ 5.95 (t, *J* = 2.8 Hz, 1H), 3.51−3.43 (m, 2H), 3.41 (d, *J* = 13.2 Hz, 1H), 3.32−3.28 (m, 1H), 2.65 (dd, *J* = 17.6, 2.8 Hz, 1H), 2.53 (dd, *J* = 17.6, 2.8 Hz, 1H), 2.06−1.78 (m, 4H), 1.60−1.42 (m, 10H); ^{13}C NMR ($CDCl_3$, 125 MHz, 50 °C) δ 162.4, 155.4, 146.7, 111.2, 85.9, 80.2, 51.4, 43.7, 39.3, 35.5, 28.5, 22.4; IR (neat) 3480, 2950, 1693, 1633 cm^{-1}; HRMS (ESI-TOF) *m*/*z* calcd for $(M + H - Boc)^+$ $(C_9H_{14}NO_3)^+$ 184.0974, found 184.0961.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Complete discussion of stereochemistry of **10a** and **10b** by 3D NMR spectroscopy, cif files, and X-ray structures of compounds **19a** and **22a**, and ^{1}H and ^{13}C NMR spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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