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The Synthesis of Methyl-Substituted Spirocyclic Piperidine-Azetidine (2,7-Diazaspiro[3.5]nonane) and Spirocyclic Piperidine-Pyrrolidine (2,8-Diazaspiro[4.5]decane) Ring Systems

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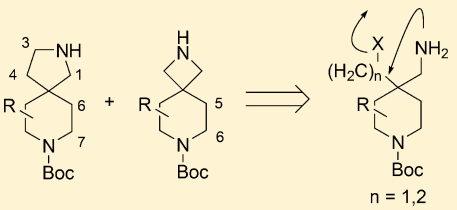
Supporting Information

ABSTRACT: The synthesis of a series of pharmaceutically important *N*-protected methyl-substituted spirocyclic piperidine-azetidine (2,7-diazaspiro[3.5]-nonane) and spirocyclic piperidine-pyrrolidine (2,8-diazaspiro[4.5]decane) ring systems was developed. These motifs contain two differentiated sites (protected secondary amines) to allow for further functionalization via reductive amination, amidation, or other chemistry. The methyl-substituted spiroazetidine ring systems were accessed using nitrile lithiation/alkylation chemistry while the methyl-substituted spiropyrrolidines were synthesized by 1,4-addition reactions with nitroalkanes, followed by reduction and cyclization. These conditions were then scaled for the synthesis of 1-methyl spirocyclic piperidine-pyrrolidine with a classical resolution of the product using a tartaric acid derivative to isolate a single enantiomer.



INTRODUCTION

In recent years, pharmaceutical interest in chemical structures with enhanced three-dimensional shapes has been increasing, leading, for example, to the replacement of aromatic rings with saturated rings.[1] The enhanced three-dimensionality (as often measured by Fsp^3, or fraction of sp^3 hybridized carbon atoms) correlates with more desirable physicochemical and biological properties, including improved solubility, permeability, and off-target promiscuity.[2a,b] Recently, the spirocyclic ring subset of saturated ring systems was reviewed by Carreira and Fessard.[3] In addition to examining reported syntheses, they enumerated specific combinations of structural properties that make spirocyclic systems of particular interest to medicinal chemists.[3] Compared to an analogous monocyclic ring system with the same number of (non-hydrogen) atoms, a spirocyclic ring system tends to have decreased lipophilicity and fewer low-energy conformations for the ring system and its substituents.[3] Decreased lipophilicity typically correlates with more desirable pharmacokinetic and safety properties in drug candidates.[4] Fewer available low-energy conformations and an overall better-defined shape of compound can lead to a decreased entropic penalty for binding a protein target when properly tuned. Furthermore, spirocyclic ring systems are much less well-known in the synthetic and medicinal chemistry literature than the corresponding monocyclic (and in some cases, fused) ring systems, providing an area of relatively novel chemical space for seeking drug candidates.[3] Consequently, spirocyclic ring systems have been used as both "cores" in medicinal chemistry, with two or more substituents projecting from the spirocycle to define much of the molecule's overall shape, and as "appendages" attached to a core for modulation of physicochemical or biological properties (see, for example, the compounds in Figure 1). In recent years, pharmacologically active spirocyclic derivatives have been reported with activities against many different biological target types,[5] including receptors, enzymes, and protein−protein interactions, and with therapeutic indications such as acute thrombosis,[6] de novo lipogenesis,[7] hypertension,[8] obesity,[9] neuropathic pain,[10] and tumor growth.[11]

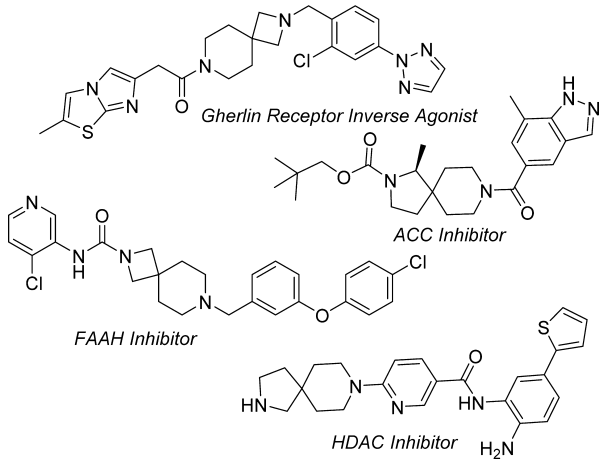


Figure 1. Examples of biologically active spirodiamines.

In several recent medicinal chemistry projects, we have had interest in spirocyclic cores. Spirocyclic diamines, in particular, have been attractive due to the varied structure types that can be accessed from differentially protected diamines by means of

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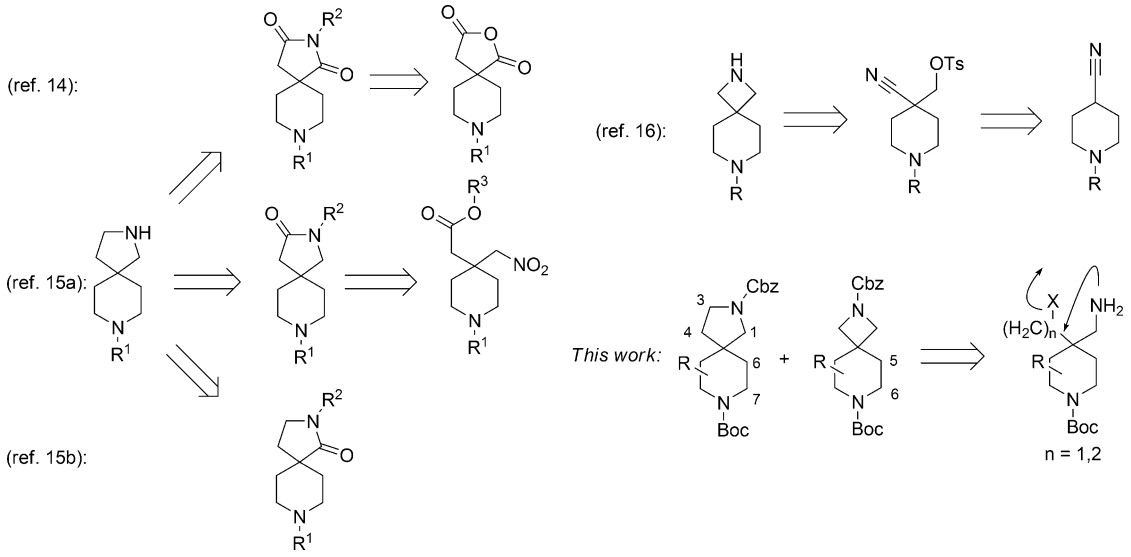
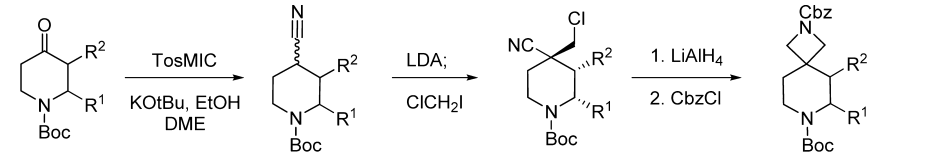


Figure 2. General strategies for spirodiamine syntheses.

Scheme 1. Synthesis of 5- and 6-Methyl Spirocyclic Piperidine-Azetidine



1a: R^1 = Me, R^2 = H
1b: R^1 = H, R^2 = Me

2a: R^1 = Me, R^2 = H, 59%
2b: R^1 = H, R^2 = Me, 71%

3a: R^1 = Me, R^2 = H, 57%
3b: R^1 = H, R^2 = Me, 85%

4a: R^1 = Me, R^2 = H (51%, two steps)
4b: R^1 = H, R^2 = Me (26%, two steps)

well-established, robust synthetic chemistry. Many unsubstituted (other than on nitrogen) spirocyclic diamine cores are known in the literature and some are commercially available,[3,5,12,13] but very few robust synthetic routes to cores with further substitution are available. We had particular interest in developing synthetic routes to methyl-substituted spirocyclic diamines in order to more thoroughly examine this chemical space for high-binding affinity to our protein targets. The methyl group as a substituent on the spirocyclic diamine core could lead to improved binding potency through hydrophobic or van der Waals interactions with the target protein;[14] it would also serve as a probe of one of the unique vectors for substitution[3] that spirocycles offer and might lead to the subsequent introduction of larger groups at that position. In some cases, methyl substitution was expected to alter the conformational preference of the already restricted parent spirocyclic ring systems.[15] More consistently, methyl substitution adjacent to a nitrogen was expected to bias conformation[16] of the *N*-substituent and possibly to diminish the desolvation energy of the final compound upon binding to the protein.[14,17] We describe here the development of robust synthetic routes to a series of methyl-substituted spirocyclic diamines that complement the known routes to unsubstituted diamine cores.

The literature syntheses of the unsubstituted spiropyrrolidine and spiroazetidine systems employ methods that are not readily adaptable to incorporation of alkyl substituents onto the rings. The synthesis of the simple spirocyclic piperidine-pyrrolidine ring system was first reported via reduction of an imide with diborane[18] and later via reduction of a lactam with borane[19a] or with lithium aluminum hydride[19b] which suffered from low yields and incompatibility with many common protecting groups (Figure 2). The synthesis of the related simple spirocyclic piperidine-azetidine utilized an aldol addition with formaldehyde, tosylation, and then a reduction/cyclization sequence to construct the azetidine ring (Figure 2).[20] While straightforward, the reported yields were low and the sequences offered room for improvement.

Our goal was to demonstrate a practical approach to the piperidino-spiroamine subset of spirocycles with appended methyl substituents. Herein are presented methods to access methyl-substituted spirocyclic piperidine-pyrrolidine and spirocyclic piperidine-azetidine systems starting from commercially available *N*-Boc-4-piperidones and employing late-stage ring closures that could be amenable to introduction of other alkyl chains in an analogous fashion (Figure 2). Additionally, the synthesis of the 1-methyl-spirocyclic piperidine-pyrrolidine was demonstrated on a larger scale without the need for chromatography. A single enantiomer was isolated using a classical resolution with a tartaric acid derivative.

RESULTS AND DISCUSSION

The synthesis of 6-methyl-substituted spirocyclic piperidine-azetidine was undertaken by utilizing a similar disconnection to the previous reports,[20] but with introduction of some improvements. Starting from 2-methyl-*N*-Boc-4-piperidone (**1a**), toluenesulfonylmethyl isocyanide (TosMIC) was first used to homologate the ketone to cyanopiperidine **2a** (Scheme 1) as a >6:1 (*trans*:*cis*) mixture. The major diastereomer was assigned through observation of a characteristic NOE enhance-

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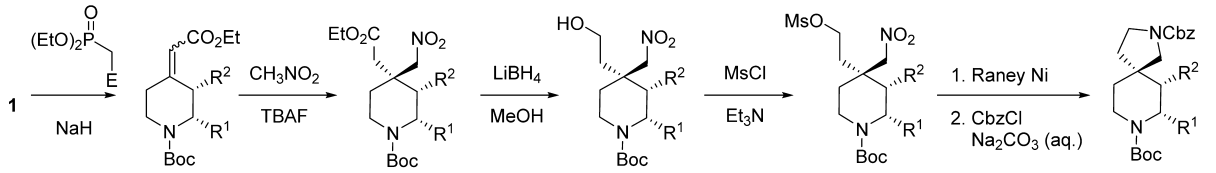
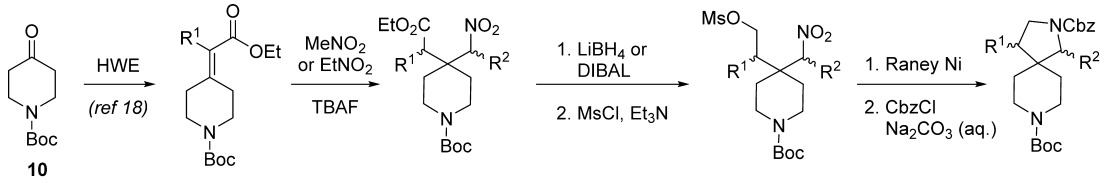
Scheme 2. Synthesis of 6- and 7-Methyl Spirocyclic Piperidine-Pyrrolidine



5a: R^1 = Me, R^2 = H, 78%
5b: R^1 = H, R^2 = Me, 97%
6a: R^1 = Me, R^2 = H, 66%
6b: R^1 = H, R^2 = Me, 71%
7a: R^1 = Me, R^2 = H, 48%
7b: R^1 = H, R^2 = Me, 46%
8a: R^1 = Me, R^2 = H, 73%
8b: R^1 = H, R^2 = Me, 89%
9a: R^1 = Me, R^2 = H (60%, two steps)
9b: R^1 = H, R^2 = Me (70%, two steps)

Scheme 3. Synthesis of 1- and 4-Methyl Spirocyclic Piperidine-Pyrrolidine



11a: R^1 = Me
11b: R^1 = H
12a: R^1 = Me, R^2 = H, 66%
12b: R^2 = H, R^2 = Me, 70%
13a: R^1 = Me, R^2 = H (54%, two steps)
13b: R^1 = H, R^2 = Me (60%, two steps)
14a: R^1 = Me, R^2 = H (89%, two steps)
14b: R^1 = H, R^2 = Me (61%, two steps)

ment between all axial hydrogens at the 2-, 4-, and 6-positions.[21] In order to avoid using the difficult-to-handle formaldehyde in an aldol addition and then activation of the hydroxyl group in a separate step,[20] the nitrile was then treated with lithium diisopropylamide (LDA) and its anion instead quenched with chloroiodomethane to directly provide the activated chloro-nitrile **3a** as the *trans* isomer. This was assigned based upon observed NOE enhancements: between the 2-methyl group and 6-hydrogen$_{axial}$ to identify the 2-methyl in an axial position, and between the 4-chloromethyl group and all 3- and 5-substituents to identify the 4-chloromethyl in an equatorial position.[21] Upon treatment with lithium aluminum hydride (LAH), the nitrile group was reduced to the amine and subsequent in situ intramolecular cyclization occurred to provide the desired spiroazetidine in a short sequence. A benzyl carbamate group (Cbz) was then installed to produce the desired 6-methyl-substituted spiroazetidine **4a**[22] and to aid in isolation as well as provide added utility with orthogonal protecting groups. Starting from 3-methyl-*N*-Boc-4-piperidone (**1b**), the same sequence was demonstrated to form the desired 5-methyl-substituted spiroazetidine **4b**, forming intermediate **2b** as an inseparable mixture of diastereomers and **3b** as the *trans* isomer. NMR analysis of **3b** revealed an equatorial 3-methyl group as determined by coupling constant analysis. An NOE enhancement was observed between the 4-chloromethyl and all 3- and 5-substituents identifying the 4-chloromethyl in an equatorial position, thus the *trans* isomer.[21] The yield of the reduction of **3b** suffered, however, as compared to the des-methyl substrate[23] and to **3a**, likely due to the increased steric bulk from the 3-methyl substituent proximal to the nitrile. Efforts to modify the reducing agent and reaction conditions were unsuccessful in finding a reaction to supersede the original result.

To form the 6-methyl and 7-methyl spiropyrrolidines, a similar disconnection involving late-stage reduction and cyclization was envisioned (Scheme 2). Starting from the commercially available 2-methyl-*N*-Boc-4-piperidone (**1a**), the ketone was converted into α,β-unsaturated ester **5a** via standard Horner–Wadsworth–Emmons conditions in good yields. Subsequent 1,4-addition of nitromethane was selective for the *trans* diastereomer (>19:1), providing nitro ester **6a**.[24] Reduction using lithium borohydride ($LiBH_4$) and methanol led to desired alcohol **7a**, which could be separated to isolate the major diastereomer via simple chromatography at this stage. The hydroxyl group was subsequently activated with methanesulfonyl chloride to provide **8a**. NMR studies were used to confirm the *trans* stereochemistry at this stage as NOE enhancements were observed between the 2-methyl group, 4-CH_2CH_2OMs group, and 6-hydrogen$_{axial}$.[21] Reduction and cyclization of **8a**, followed by Cbz protection, then provided the protected spiropyrrolidine **9a**.[22] An analogous sequence starting from 3-methyl-*N*-Boc-4-piperidone (**1b**) led to desired nitroalkane **6b** (>5:1 *trans*:*cis*) with less selectivity as compared to **6a**. The major diastereomer was then separated after reduction. NMR analysis of **7b** revealed an equatorial 3-methyl group using coupling constant analysis, and an NOE enhancement was observed between 4-nitromethyl and all 3- and 5-substituents identifying the 4-nitromethyl in an equatorial position and, therefore, showing *trans* stereochemistry.[21] **7b** was then taken through the remainder of the route to provide the desired 7-methyl spiropyrrolidine **9b**.

This method was then extended to incorporate methyl substitution on the pyrrolidine rings. The synthesis of protected 1-methyl spirocyclic piperidine-pyrrolidine began with the commercially available α,β-unsaturated ester **11a** derived from *N*-Boc-piperidone (**10**, Scheme 3). Addition of nitroethane in the presence of tetrabutylammonium fluoride (TBAF) as base led to 1,4-addition and the formation of nitro ester **12a**. Reduction of the ethyl ester with $LiBH_4$ occurred in moderate yield to provide the alcohol, which was then activated to form mesylate **13a**. Hydrogenolysis with Raney Nickel effected reduction, and then cyclization occurred in situ to form the spiropyrrolidine. To afford differential protection, the amine was again directly converted into the benzyl carbamate **14a**. This sequence was then applied to the synthesis of the 4-methyl spiropyrrolidine by first introducing the methyl group via

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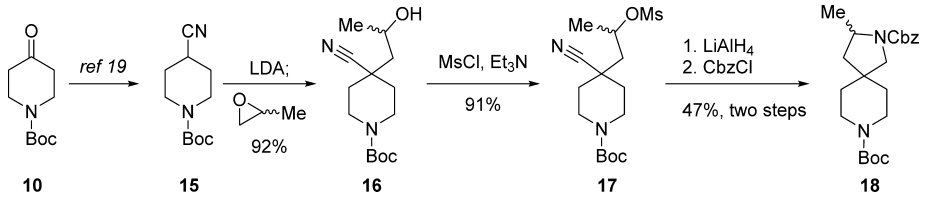
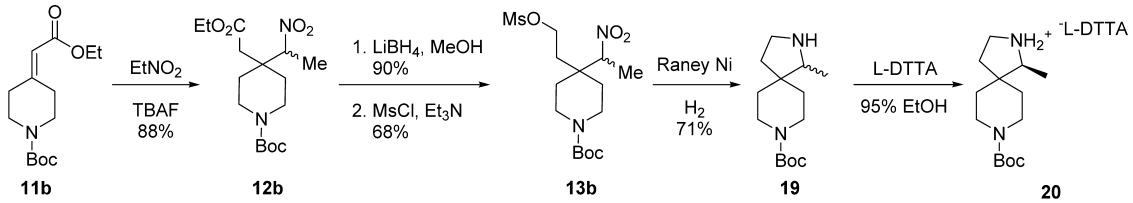
Scheme 4. Synthesis of 3-Methyl Spirocyclic Piperidine-Pyrrolidine



Scheme 5. Classical Resolution of 1-Methyl Spirocyclic Piperidine-Pyrrolidine



Horner–Wadsworth–Emmons reaction[25] to form **11b** and employing nitromethane in the subsequent 1,4-addition step. The steric bulk adversely affected the $LiBH_4$ reduction of the now α-substituted ester **12b**, and initially, low conversions were observed. Switching to the more reactive diisobutylaluminum hydride (DIBAL) proved a reasonable alternative to provide the desired alcohol. Mesylation to **13b**, nitro reduction, cyclization, and Cbz protection then afforded the desired carbamate **14b**.

To synthesize the 3-methyl spirocyclic piperidine-pyrrolidine, a similar final disconnection to the other four spirocyclic piperidine-pyrrolidine targets was employed, but due to the desired placement of the methyl group, an alternate starting material was chosen. Commercially available cyano-piperidine **15** (which can be formed from **10**)[26] was deprotonated by the action of LDA, and the resultant anion was quenched with (±)-propylene oxide to provide the desired alcohol **16** in high yield (Scheme 4). Treatment of the alcohol with methanesulfonyl chloride then led to mesylate **17**. Reduction of the nitrile was effected by treatment with $LiAlH_4$ with in situ cyclization to form the spiropyrrolidine ring. Finally, protection and isolation led to benzyl carbamate **18**.

In order to demonstrate the practical nature of the chemistry presented, the synthesis of 1-methyl spirocyclic piperidine-pyrrolidine was executed on a larger scale (Scheme 5). During the optimization of this sequence, several steps were telescoped and yields were improved (**11b** to **12b**: 88% vs 70%, reduction of **12b**: 90% vs 73%). The conversion to mesylate **13b** was also high, and pure material was isolated in 68% yield following crystallization to avoid chromatography to produce 150 g of material. Hydrogenation and in situ cyclization occurred to give crude material in 71% yield. A portion of this material was then treated with (−)-*O*,*O*-di-*p*-toluoyl-L-tartaric acid (L-DTTA) in an unoptimized classical resolution to provide high purity and 98.9% ee. An X-ray quality single crystal was then grown and analyzed to determine the absolute configuration of the methyl substituent as *S* (Figure 3).

In conclusion, methods were developed to synthesize a series of methyl-substituted spirocyclic piperidine-pyrrolidines and piperidine-azetidines with orthogonal protecting groups enabling further functionalization. Considering the common ketone starting material employed, this methodology could likely be extended to allow access to spiroazetidines and spiropyrrolidines of various other ring sizes and substitution patterns.

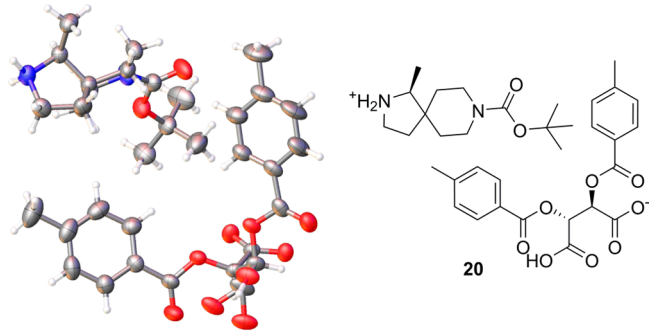


Figure 3. Single-crystal X-ray diagram drawn at 50% probability.

EXPERIMENTAL PROCEDURES

General Methods. All chemicals, reagents, and solvents were purchased from commercial sources when available and used without further purification. Air- and moisture-sensitive reactions were carried out under an inert atmosphere of nitrogen, magnetically stirred, and monitored by thin-layer chromatography (TLC) using precoated 250 μm silica gel plates and visualized by fluorescence quenching under UV light or with ceric ammonium molybdate, polymolybdic acid, or ninhydrin stains. Unless stated otherwise, reactions were carried out at room temperature (~23 °C). Silica gel chromatography was performed using an automated system using prepackaged columns. Concentration under reduced pressure (in vacuo) was performed by rotary evaporation at 25–35 °C at appropriate pressure. Purified compounds were further dried under high vacuum to remove residual solvent. Yields refer to purified compounds. NMR spectra were recorded with either a spectrometer at 600 and 151 MHz or a spectrometer at 400 and 100 MHz for ^{1}H, ^{13}C acquisitions, respectively. Chemical shifts were referenced to the residual ^{1}H solvent signals ($CDCl_3$, δ 7.27, DMSO-d_6, δ 2.50; CD_3OD, δ 3.31; CD_3CN, δ 1.94) and solvent ^{13}C signals ($CDCl_3$, δ 77.0; DMSO-d_6, δ 39.51; CD_3OD, δ 49.15). Signals are listed as follows: chemical shift in ppm (multiplicity identified as s = singlet, br = broad, d = doublet, t = triplet, q = quartet, quin = quintuplet, m = multiplet; coupling constants in Hz; integration). High-temperature NMR analysis was performed in some cases due to rotamerism-induced peak broadening observed at rt to provide more useful data. High-resolution mass spectrometry (HRMS) was performed via atmospheric pressure chemical ionization (APCI) or electrospray ionization (ESI) sources.

***tert*-Butyl *trans*-4-Cyano-2-methylpiperidine-1-carboxylate (2a).** A round-bottom flask was charged with *tert*-butyl 2-methyl-4-

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oxopiperidine-1-carboxylate (3.00 g, 14.0 mmol), toluenesulfonylmethyl isocyanide (3.40 g, 17.4 mmol), ethanol (1.4 mL, 24 mmol), and 1,2-dimethoxyethane (100 mL) and cooled to 0 °C. Potassium *tert*-butoxide (1.0 M in THF, 36 mL, 36 mmol) was then added dropwise, and the reaction was stirred at 40 °C for 16 h. The reaction was filtered through Celite and washed with diethyl ether. The filtrate was concentrated in vacuo, and flash column chromatography (20% to 50% ethyl acetate/heptane) was used to provide 1.87 g (59% yield) of a >6:1 mixture of diastereomers of the title compound as a colorless oil that solidified upon standing. Note: A small sample was purified by reverse phase HPLC; then NMR studies revealed the major diastereomer to be the *trans* isomer. See the SI for more details.

^{1}H NMR (400 MHz, $CDCl_3$) δ *major*: 4.52−4.42 (m, 1H), 4.06−3.96 (m, 1H), 2.86−2.70 (m, 2H), 2.04−1.96 (m, 1H), 1.94−1.81 (m, 2H), 1.64 (dq, J = 4.5, 12.8 Hz, 1H), 1.43 (s, 9H), 1.11 (d, J = 7.0 Hz, 3H). *minor*: 4.42−4.33 (m, 1H), 4.05−3.95 (m, 1H), 3.19−3.10 (m, 1H), 2.94−2.88 (m, 1H), 2.78−2.71 (m, 1H), 2.02−1.60 (m, 2H), 1.73 (td, J = 5.1, 13.3 Hz, 1H), 1.46 (s, 9H), 1.36 (d, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ *major*: 154.2, 121.7, 79.9, 44.8, 37.0, 33.4, 29.0, 28.3, 22.1, 15.3. *minor*: 154.4, 122.5, 79.8, 45.5, 34.8, 31.2, 28.3, 27.7, 21.8, 16.9. HRMS (m/z): calc. for $C_{12}H_{20}N_2O_2$ $[M + Na]^+$: 247.1417; found: 247.1413.

***tert*-butyl *trans*-4-(Chloromethyl)-4-cyano-2-methylpiperidine-1-carboxylate (3a).** A 100 mL oven-dried, 3-neck round-bottom flask was equipped with a thermometer and nitrogen inlet. Diisopropylamine (2.0 mL, 14 mmol) was added along with tetrahydrofuran (12 mL). The mixture was cooled to −6 °C in a brine-ice bath. *n*-Butyl lithium in hexanes (2.5 M in hexanes, 5.80 mL, 11.6 mmol) was then added over 10 min. The reaction was cooled to −65 °C, and *tert*-butyl 4-cyano-2-methylpiperidine-1-carboxylate (1.65 g, 7.40 mmol) was added in tetrahydrofuran (2 mL) over 5 min. The reaction was stirred at an internal temperature between −45 and −50 °C for 25 min. The solution turned to a pale, brown suspension and was stirred for another 20 min before cooling to −60 °C. Chloroiodomethane (0. 94 mL, 13 mmol) was then added over 1 min. The temperature was maintained below −19 °C during addition, and the suspension turned to an orange solution once the addition was complete. The reaction mixture was allowed to warm to rt, and stirring was continued for 16 h. The reaction was cooled to −10 °C and then quenched with water (6 mL) and diluted with diethyl ether. The layers were separated, and the aqueous layer was extracted with diethyl ether. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuo. Flash column chromatography (20% to 50% ethyl acetate/heptanes) was then used to provide 1.15 g (57% yield) of the title compound as an orange oil. NMR studies show the 4-chloromethyl and 2-methyl groups with *trans* relative stereochemistry. See the SI for more details.

^{1}H NMR (400 MHz, DMSO, 353 K) δ 4.40 (quin, J = 6.7 Hz, 1H), 4.01 (td, J = 3.5, 14.4 Hz, 1H), 3.78 (s, 2H), 3.06 (dt, J = 2.6, 13.9 Hz, 1H), 2.13−2.00 (m, 2H), 1.72 (dd, J = 6.4, 14.2 Hz, 1H), 1.50 (dt, J = 4.5, 13.4 Hz, 1H), 1.43 (s, 9H), 1.32 (d, J = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, DMSO, 353 K) δ 153.2, 121.7, 78.7, 50.1, 44.6, 36.2, 35.2, 34.9, 31.8, 27.7, 16.0. HRMS (m/z): calc. for $C_{13}H_{21}ClN_2O_2$ $[M + Na]^+$: 295.1184; found: 295.1182.

2-Benzyl 7-(*tert*-Butyl) 6-Methyl-2,7-diazaspiro[3.5]nonane-2,7-dicarboxylate (4a). A round-bottom flask was charged *tert*-butyl 4-(chloromethyl)-4-cyano-2-methylpiperidine-1-carboxylate (345 mg, 1.26 mmol) in tetrahydrofuran (8 mL) and cooled to 0 °C. Lithium aluminum hydride in tetrahydrofuran (2M, 2.5 mL, 5.0 mmol) was added. The cooling bath was removed, and the reaction was stirred at rt for 5 h. The reaction was cooled to −5 °C; then water (1.0 mL) was added, followed by 1 M aqueous sodium hydroxide (1.0 mL). The reaction was stirred for 1 h at 0 °C; then the suspension was filtered through Celite and washed with diethyl ether. The filtrate was then washed with brine, dried over magnesium sulfate, filtered, and concentrated in vacuo to provide 259 mg of crude *tert*-butyl 6-methyl-2,7-diazaspiro[3.5]nonane-7-carboxylate (85% yield) as a colorless oil that was brought forward without further purification.

A round-bottom flask was charged with *tert*-butyl 6-methyl-2,7-diazaspiro[3.5]nonane-7-carboxylate (240 mg, 1.0 mmol) and methylene chloride (5 mL). Triethylamine (0.30 mL, 2.2 mmol) was added, and the reaction was stirred at 40 °C for 30 min. The reaction was cooled to rt, benzyl chloroformate (80 μL, 0.56 mmol) was added, and the reaction was stirred at rt for 1 h. The reaction was diluted with ethyl acetate, and the mixture was washed with 1 M aqueous sodium hydroxide (5 mL) and brine (5 mL), dried over magnesium sulfate, filtered, and concentrated in vacuo. Flash column chromatography (20% to 50% ethyl acetate/heptane) was then used to provide 225 mg (60% yield) of the title compound as a colorless gum.

^{1}H NMR (400 MHz, DMSO-d_6, 325 K) δ 7.45−7.23 (m, 5H), 5.03 (s, 2H), 4.25 (quind, J = 6.8, 1.6 Hz, 1H), 3.83 (s, 2H), 3.78 (ddd, J = 2.3, 4.7, 13.8 Hz, 1H), 3.63 (d, J = 8.2 Hz, 1H), 3.53 (d, J = 8.2 Hz, 1H), 2.90 (dt, J = 2.6, 13.4 Hz, 1H), 1.83 (d, J = 13.7 Hz, 2H), 1.61 (dd, J = 6.0, 13.9 Hz, 1H), 1.47 (dt, J = 5.1, 13.1 Hz, 1H), 1.39 (s, 9H), 1.02 (d, J = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6, 353 K) δ 155.5, 153.5, 136.6, 127.9, 127.3, 127.1, 78.1, 65.3, 60.4, 58.8, 45.6, 37.9, 34.8, 34.4, 31.9, 27.7, 16.4. HRMS (m/z): calc. for $C_{21}H_{30}N_2O_4$ $[M + Na]^+$: 397.2098; found: 397.2095.

***tert*-Butyl 4-Cyano-3-methylpiperidine-1-carboxylate (2b).** A round-bottom flask was charged with *tert*-butyl 3-methyl-4-oxopiperidine-1-carboxylate (1.0 g, 4.7 mmol), toluenesulfonyl methyl isocyanide (1.20 g, 6.10 mmol), and DME (10 mL) and then cooled to 0 °C. Potassium *tert*-butoxide (1.26 g, 11.3 mmol) was then added, and the reaction was allowed to warm to rt. The reaction was stirred for 2 h and then quenched with the addition of water and diluted with ethyl acetate. The layers were separated, and the aqueous was extracted with ethyl acetate × 3. The combined organic layers were then dried over sodium sulfate, filtered, and concentrated in vacuo. Flash column chromatography was then used to provide 730 mg (71%) of an ∼1.3:1 inseparable mixture of diastereomers of the title compound (oil).

Note: The relative stereochemistry of the major diastereomer could not be determined due to the low selectivity and deprotonation that takes place in the next step. Partial integrals are reported in the line list as a result (please see the SI for spectra).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.12−3.94 (m, J = 12.9 Hz, 1.2H), 3.90 (dt, J = 14.0 Hz, 3.9 Hz, 0.5H), 3.86−3.75 (br. s, 0.3 H), 3.11 (ddd, J = 2.9, 11.4, 14.1 Hz, 0.4H), 2.91 (q, J = 4.0 Hz, 0.4H), 2.87−2.78 (m, 0.4H), 2.74 (ddd, J = 2.9, 11.6, 14.0 Hz, 0.6H), 2.42 (br. s, 0.6H), 2.22 (dt, J = 3.9, 10.9 Hz, 0.6H), 2.01 (qd, J = 3.3, 13.5 Hz, 0.6H), 1.92 (qd, J = 3.6, 13.8 Hz, 0.4H), 1.88−1.64 (m, 2H), 1.44 (s, 9H), 1.10 (d, J = 6.6 Hz, 1.8H), 1.07 (d, J = 6.6 Hz, 1.2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.4, 154.2, 120.8, 119.3, 80.1, 79.9, 49.2, 46.9, 42.4, 40.2, 34.5, 33.9, 32.8, 32.0, 28.5, 28.3, 28.3, 27.6, 17.0, 16.1 (2 sets of peaks reported due to diastereomeric mixture present). HRMS (m/z): calc. for $C_{12}H_{20}N_2O_2$ $[M + Na]^+$: 247.1417; found: 247.1417.

***tert*-Butyl *trans*-4-(Chloromethyl)-4-cyano-3-methylpiperidine-1-carboxylate (3b).** A round-bottom flask was charged with THF (20 mL) and diisopropylamine (0.98 mL, 6.9 mmol) and then cooled to −78 °C. *n*-Butyllithium was added dropwise; then the reaction was stirred for 5 min before warming to 0 °C for 10 min. The reaction was cooled to −50 °C; then *tert*-butyl 4-cyano-3-methylpiperidine-1-carboxylate (1.03 g, 4.59 mmol) was added slowly via cannula as a solution in THF (2 mL) and stirred for 1 h at −50 °C. Chloroiodomethane (0.75 mL, 10 mmol) was added dropwise and stirred for 1 h at −50 °C and then warmed to 0 °C for 1 h. The reaction was quenched with the slow addition of saturated ammonium chloride solution and diluted with ethyl acetate. The layers were separated, and the aqueous was extracted with ethyl acetate (×3). The combined organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo. Flash column chromatography was then used to provide 1.06 g (85% yield) of the title compound as a pale yellow oil. NMR studies show the 4-chloromethyl and 3-methyl groups with *trans* relative stereochemistry. See the SI for more details.

^{1}H NMR (400 MHz, DMSO-d_6, 353 K) δ 4.07 (d, J = 11.3 Hz, 1H), 4.03 (dddd, J = 1.6, 2.7, 4.3, 14.0 Hz, 1H), 3.89 (ddd, J = 1.8, 4.2, 14.0 Hz, 1H), 3.80 (d, J = 11.7 Hz, 1H), 2.92 (ddd, J = 2.7, 12.5, 14.0 Hz, 1H), 2.62 (dd, J = 11.1, 13.9 Hz, 1H), 2.11 (td, J = 2.8, 13.9 Hz, 1H), 1.80 (dqd, J = 4.1, 6.7, 11.0 Hz, 1H), 1.60 (ddd, J = 4.7, 12.3, 13.9 Hz, 1H), 1.43 (s, 10H), 1.03 (d, J = 6.6 Hz, 3H). ^{13}C NMR (101 MHz,

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DMSO-d_6, 353 K) δ 153.1, 118.2, 78.8, 47.5, 46.6, 44.5, 40.1, 34.8, 31.2, 27.6, 13.0. HRMS (m/z): calc. for $C_{13}H_{21}ClN_2O_2$ $[M + Na]^+$: 295.1184; found: 295.1181.

2-Benzyl 7-(*tert*-Butyl) 5-Methyl-2,7-diazaspiro[3.5]nonane-2,7-dicarboxylate (4b). A round-bottom flask was charged with *tert*-butyl 4-(chloromethyl)-4-cyano-3-methylpiperidine-1-carboxylate (593 mg, 2.20 mmol) and THF (4 mL) and then cooled to −5 °C. Lithium aluminum hydride (2 M in THF, 3.0 mL, 6.0 mmol) was added dropwise over 5 min. The internal temperature stayed below 0 °C during the addition. The cooling bath was removed, and the reaction was stirred at rt for 3 h. The reaction mixture was cooled to 0 °C; then water (3.0 mL) was added, followed by 1 N sodium hydroxide (3.0 mL). The internal temperature was maintained below 3 °C during the addition. The reaction mixture was stirred at 0 °C for 30 min and then filtered through Celite and washed with diethyl ether (50 mL). The filtrate was concentrated and dried under high vacuum to provide crude *tert*-butyl 5-methyl-2,7-diazaspiro[3.5]nonane-7-carboxylate (361 mg) as a clear, yellow oil that was taken onto the next step without additional purification.

A round-bottom flask was charged with *tert*-butyl 5-methyl-2,7-diazaspiro[3.5]nonane-7-carboxylate (350 mg, 1.5 mmol), dichloromethane (5 mL), and triethylamine (300 μL, 2.2 mmol). Benzyl chloroformate (220 uL, 1.5 mmol) was added, and the reaction was stirred at rt for 16 h. Ethyl acetate (30 mL) was added, and the layers separated. The organic layer was washed with 1 N sodium hydroxide (5 mL), then brine (5 mL), and dried over magnesium sulfate, filtered, and concentrated in vacuo. Flash column chromatography (20% to 50% ethyl acetate in heptanes) was then used to provide the title compound (205 mg, 26% over two steps) as a colorless gum.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.25 (m, 5H), 5.05 (s, 2H), 3.76 (d, J = 9.0 Hz, 2H), 3.63 (d, J = 8.2 Hz, 1H), 3.52 (d, J = 8.6 Hz, 1H), 3.33 (ddd, J = 4.3, 7.0, 13.7 Hz, 1H), 3.27−3.17 (m, 2H), 3.05 (dd, J = 6.6, 12.5 Hz, 1H), 1.87−1.67 (m, 2H), 1.55 (ddd, J = 3.9, 6.9, 13.4 Hz, 1H), 1.41 (s, 9H), 0.88 (d, J = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.4, 153.8, 136.6, 127.9, 127.3, 127.0, 78.1, 65.3, 57.4, 55.0, 45.5, 40.0, 36.8, 35.2, 32.2, 27.7, 11.4. HRMS (m/z): calc. for $C_{20}H_{30}N_2O_4$ $[M + Na]^+$: 397.2098; found: 397.2098.

***tert*-Butyl 4-(2-Ethoxy-2-oxoethylidene)-2-methylpiperidine-1-carboxylate (5a).** A round-bottom flask was charged with sodium hydride (60% in mineral oil, 204 mg, 5.11 mmol) and tetrahydrofuran (36 mL) and then cooled to 0 °C. Triethylphosphonoacetate (1.16 g, 5.16 mmol) was added dropwise. The reaction was stirred for 15 min at 0 °C and then warmed to rt for 30 min. The reaction was cooled to 0 °C; then *tert*-butyl 2-methyl-4-oxopiperidine-1-carboxylate (1.00 g, 4.70 mmol) was added dropwise as a solution in 5 mL of tetrahydrofuran. The reaction was stirred at 0 °C for 4 h. The reaction was quenched with the careful addition of saturated ammonium chloride solution and diluted with ethyl acetate. The layers were separated, and the aqueous was extracted with ethyl acetate (×3). The combined organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo. Flash column chromatography was then used to provide 1.04 g (78% yield) of the title compound as an ~2.3:1 inseparable mixture of olefin isomers (oil).

Note: Because of the isomeric mixture, partial integrals are reported.

^{1}H NMR (400 MHz, DMSO-d_6, 353 K) δ 5.84 (s, 0.3H), 5.73 (s, 0.7H), 4.45−4.41 (m, 0.3H), 4.38−4.25 (m, 0.7H), 4.11 (q, J = 7.2 Hz, 2H), 3.98−3.92 (m, 0.3H), 3.87 (ddd, J = 3.1, 5.9, 13.3 Hz, 0.7H), 3.46 (dd, J = 2.3, 13.7 Hz, 0.3H), 3.36 (td, J = 3.5, 15.3 Hz, 0.7H), 3.02−2.90 (m, 1H), 2.55−2.49 (m, 0.6H), 2.32−2.22 (m, 1.7H), 2.18 (dd, J = 3.5, 13.7 Hz, 0.7H), 1.42 (s, 9H), 1.25−1.18 (m, 3H), 1.04 (d, J = 6.6 Hz, 2.1H), 1.01 (d, J = 7.0 Hz, 0.9H).^{13}C NMR (101 MHz, DMSO-d_6, 353 K) δ 165.1, 164.8, 155.8, 155.4, 153.4, 153.4, 116.1, 115.8, 78.4, 78.4, 58.7, 47.2, 47.0, 37.9, 34.9, 33.6, 28.7, 27.7, 16.9, 16.3, 13.7. HRMS (m/z): calc. for $C_{15}H_{25}NO_4$ $[M + Na]^+$: 306.1676; found: 306.1678.

***tert*-Butyl *trans*-4-(2-Ethoxy-2-oxoethyl)-2-methyl-4-(nitromethyl)piperidine-1-carboxylate (6a).** A round-bottom flask was charged with *tert*-butyl 4-(2-ethoxy-2-oxoethylidene)-2-methylpiperidine-1-carboxylate (500 mg, 1.76 mmol) and THF (10 mL). Nitromethane (0.44 mL, 7.8 mmol) was added, followed by the dropwise addition of TBAF (1.0 M in THF, 1.76 mL, 1.76 mmol). The reaction was heated to 50 °C for 5 h. The reaction was cooled to rt and quenched with half-saturated ammonium chloride solution and then diluted with ethyl acetate. The layers were separated, and the aqueous was extracted with ethyl acetate (×2). The combined organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo. The crude material was then purified using flash column chromatography (20% to 100% ethyl acetate/heptane) to provide 403 mg (66% yield) of the title compound (>19:1 *trans*:*cis*) as an oil. Relative stereochemistry was determined for **8a** due to better resolution of key signals.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.62 (d, J = 11.3 Hz, 1H), 4.53 (d, J = 11.3 Hz, 1H), 4.21 (quin, J = 6.6 Hz, 1H), 4.20−4.12 (m, 2H), 3.91 (ddd, J = 14.0, 5.5, 2.3 Hz, 1H), 2.99 (ddd, J = 4.3, 11.9, 14.2 Hz, 1H), 2.67 (d, J = 17.2 Hz, 1H), 2.57 (d, J = 17.2 Hz, 1H), 1.78−1.57 (m, 4H), 1.46 (s, 9H), 1.28 (t, J = 7.4 Hz, 3H), 1.18 (d, J = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6, 154.6, 82.2, 79.8, 60.6, 45.2, 39.7, 36.4, 35.0, 34.7, 32.4, 28.4, 19.3, 14.1. HRMS (m/z): calc. for $C_{16}H_{28}N_2O_6$ $[M + Na]^+$: 367.1840; found: 367.1837.

***tert*-Butyl *trans*-4-(2-Hydroxyethyl)-2-methyl-4-(nitromethyl)piperidine-1-carboxylate (7a).** A round-bottom flask was charged with *tert*-butyl *trans*-4-(2-ethoxy-2-oxoethyl)-2-methyl-4-(nitromethyl)piperidine-1-carboxylate (424 mg, 1.23 mmol) and tetrahydrofuran (5 mL) and then cooled to 0 °C. Lithium borohydride (2.0 M in THF, 1.23 mL, 2.46 mmol) was added. Methanol (0.10 mL, 2.5 mmol) was added dropwise, the ice bath was removed, and the reaction was stirred at rt for 15 h. The reaction was quenched by adding 10 mL of aqueous 1 M AcOH solution and stirred for 30 min. The reaction was diluted with water and ethyl acetate, and the layers separated. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were washed with 1 M NaOH solution, then brine, and dried over sodium sulfate, filtered, and concentrated in vacuo. Flash column chromatography (20% to 100% ethyl acetate/heptane) was then used to provide 178 mg (48% yield) of the title compound as an oil.

Relative stereochemistry was determined for **8a** due to better resolution of key signals.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.39 (s, 2H), 4.21 (sxt, J = 6.7 Hz, 1H), 3.94−3.77 (m, 3H), 2.99 (ddd, J = 4.7, 12.1, 14.2 Hz, 1H), 1.92−1.64 (m, 5H), 1.62−1.50 (m, 2H), 1.46 (s, 9H), 1.20 (d, J = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.7, 83.2, 79.8, 58.5, 45.4, 38.5, 36.8, 35.8, 34.9, 32.5, 28.4, 19.4. HRMS (m/z): calc. for $C_{14}H_{26}N_2O_5$ $[M + Na]^+$: 325.1734; found: 325.1736.

***tert*-Butyl *trans*-2-Methyl-4-(2-((methylsulfonyl)oxy)ethyl)-4-(nitromethyl)piperidine-1-carboxylate (8a).** A round-bottom flask was charged with *tert*-butyl *trans*-4-(2-hydroxyethyl)-2-methyl-4-(nitromethyl)piperidine-1-carboxylate (127 mg, 0.420 mmol), methylene chloride (10 mL), and triethylamine (0.23 mL, 1.7 mmol) and then cooled to 0 °C. Methanesulfonyl chloride (83 μL, 1.1 mmol) was added dropwise, and the reaction was stirred for 1 h. The reaction was quenched with aqueous sodium bicarbonate solution and stirred for 15 min at rt. The layers were separated, and the aqueous was extracted with methylene chloride × 3. The combined organic layers were further quenched with a small amount of methanol (to consume any unquenched methanesulfonyl chloride). The organic layers were then dried over sodium sulfate, filtered, and concentrated in vacuo. The crude material was then purified via flash column chromatography (20% to 80% ethyl acetate/heptane) to provide 117 mg (73% yield) of the title compound as an oil. NMR studies show the 4-nitromethyl and 2-methyl groups with *trans* relative stereochemistry. See the SI for more details.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.41 (t, J = 6.6 Hz, 2H), 4.34 (d, J = 11.7 Hz, 1H), 4.30 (d, J = 11.7 Hz, 1H), 4.20 (sxt, J = 6.8 Hz, 1H), 3.92 (ddd, J = 2.3, 5.9, 14.0 Hz, 1H), 3.04 (s, 3H), 3.00 (ddd, J = 4.7, 11.7, 14.4 Hz, 1H), 2.07−1.95 (m, 2H), 1.76 (dd, J = 6.6, 14.4 Hz, 1H), 1.72−1.64 (m, 1H), 1.63−1.49 (m, 2H), 1.46 (s, 9H), 1.20 (d, J = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.5, 82.2, 79.9, 65.1, 45.2, 37.5, 36.8, 35.7, 35.6, 34.7, 32.4, 28.4, 19.4. HRMS (m/z): calc. for $C_{15}H_{28}N_2O_7$ $[M + Na]^+$: 403.1509; found: 403.1513.

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2-Benzyl 8-(*tert*-Butyl) *trans*-7-Methyl-2,8-diazaspiro[4.5]-decane-2,8-dicarboxylate (9a). A Parr reactor was charged with *tert*-butyl *trans*-2-methyl-4-(2-((methylsulfonyl)oxy)ethyl)-4-(nitromethyl)piperidine-1-carboxylate (114 mg, 0.300 mmol) and 10 mL of ethanol. A small spatula tip of Raney Nickel 2800 slurry in water was then added, and the reactor was sealed, purged with nitrogen × 3, flushed with hydrogen × 3, and finally charged with 50 psi hydrogen. The reaction was stirred for 24 h at rt. The pressure was removed, and the reactor was flushed with nitrogen. The reaction was filtered through a pad of Celite and washed with ethanol. The filtrate was concentrated in vacuo to provide 111 mg (quant.) of a crude oil that was taken onto the next step without purification.

A round-bottom flask was charged with the crude oil, acetonitrile (2 mL), water (2 mL), and sodium carbonate (96 mg, 0.90 mmol) and then stirred vigorously. Benzyl chloroformate (85 μL, 0.60 mmol) was added dropwise, and the reaction was stirred for 5 h. The reaction was diluted with ethyl acetate and water. The layers were separated, and the aqueous was extracted with ethyl acetate × 2. The combined organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo. Flash column chromatography (20% to 75% ethyl acetate/heptane) was then used to provide 70 mg (60% yield) of the title compound as an oil.

^{1}H NMR (400 MHz, DMSO-d_6, 353 K) δ 7.40−7.26 (m, 5H), 5.07 (s, 2H), 4.15 (dquin, J = 4.2, 6.6 Hz, 1H), 3.75 (ddd, J = 3.0, 5.1, 13.7 Hz, 1H), 3.52−3.32 (m, 2H), 3.10 (q, J = 10.5 Hz, 2H), 2.98 (ddd, J = 3.9, 12.1, 14.0 Hz, 1H), 1.97 (ddd, J = 3.9, 7.4, 12.1 Hz, 1H), 1.78−1.66 (m, 2H), 1.59−1.51 (m, 1H), 1.46−1.32 (m, 2H), 1.41 (s, 9H), 1.13 (d, J = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6, 353 K) δ 153.7, 153.6, 136.8, 127.9, 127.2, 126.9, 78.0, 65.4, 58.4, 45.6, 44.5, 38.5, 37.5, 35.4, 34.5, 32.8, 27.7, 18.0. HRMS (m/z): calc. for $C_{22}H_{32}N_2O_4$ [M + Na]$^+$: 411.2254; found: 411.2254.

***tert*-Butyl 4-(2-Ethoxy-2-oxoethylidene)-3-methylpiperidine-1-carboxylate (5b).** A round-bottom flask was charged with triethylphosphonoacetate (3.10 mL, 15.6 mmol) and tetrahydrofuran (32 mL). Sodium hydride (60% dispersion in mineral oil, 670 mg, 17.0 mmol) was added at 0 °C, and the reaction was stirred for 5 min and then warmed to rt for 50 min. The reaction was cooled to 0 °C, and *tert*-butyl 3-methyl-4-oxopiperidine-1-carboxylate (3.00 g, 14.1 mmol) was added as a solution in 9 mL of tetrahydrofuran. The ice batch was removed, and the reaction was stirred at rt for 5 h. The reaction was quenched with saturated aqueous sodium bicarbonate solution and diluted with ethyl acetate. The layers were separated, and the aqueous layer was extracted with ethyl acetate × 3. The combined organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo. Flash column chromatography (0% to 100% ethyl acetate/heptanes) was then used to provide 3.88 g (97% yield) of the title compound as an inseparable ∼3:1 mixture of isomers (oil).

Note: The presence of the mixture makes it difficult to resolve and properly enumerate the line list (please see the SI for spectra), and therefore, peaks have been labeled with partial integrals:

^{1}H NMR (400 MHz, DMSO-d_6, 353 K) δ 5.70−5.61 (m, 1H), 4.16−4.07 (m, 2H), 3.88−3.77 (m, 0.5H), 3.56 (dd, J = 4.3, 12.9 Hz, 0.75H), 3.51−3.29 (m, 1.5H), 3.14−2.97 (m, 1.5H), 2.92 (dd, J = 3.9, 13.7 Hz, 0.25H), 2.80 (dt, J = 3.3, 12.4 Hz, 0.25H), 2.75−2.64 (m, 0.75H), 2.57−2.36 (m, 1.25H), 2.15 (td, J = 3.0, 14.2 Hz, 0.25H), 1.50−1.36 (m, 9H), 1.27−1.16 (m, 3H), 1.14−0.92 (m, 3H). *Contains 8 mol % ethyl acetate solvate, unable to be removed with drying.

^{13}C NMR (400 MHz, DMSO-d_6, 353 K) δ 165.3, 164.8, 161.1, 161.0, 153.9, 153.6, 114.2, 112.8, 78.5, 78.3, 58.8, 58.7, 49.9, 48.0, 43.8, 43.4, 39.6, 37.8, 31.8, 30.9, 27.7, 26.9, 16.7, 15.4, 13.62, 13.60. HRMS (m/z): calc. for $C_{15}H_{25}NO_4$ [M + Na]$^+$: 306.1676; found: 306.1670.

***tert*-Butyl *trans*-4-(2-Ethoxy-2-oxoethyl)-3-methyl-4-(nitromethyl)piperidine-1-carboxylate (6b).** A round-bottom flask was charged with *tert*-butyl 4-(2-ethoxy-2-oxoethylidene)-3-methylpiperidine-1-carboxylate (2.6 g, 9.2 mmol) and tetrahydrofuran (30 mL); then tetrabutylammonium fluoride (1 M in THF, 23 mL, 23 mmol) and nitromethane (2.3 mL, 40 mmol) in tetrahydrofuran (10 mL) were added. The reaction mixture was stirred at reflux temperature for 16 h. The reaction was quenched with saturated ammonium chloride solution (10 mL). The reaction was extracted with ethyl acetate (2 × 30 mL), and the combined organic layers were washed with brine (10 mL), dried over magnesium sulfate, filtered and concentrated in vacuo. The crude material was purified by flash column chromatography (10% to 20% ethyl acetate/heptanes) to provide 2.25 g (71% yield) of the title compound (colorless oil) as an inseparable >5:1 mixture of diastereomers.

Only peaks corresponding to the major isomer are reported:

^{1}H NMR (400 MHz, DMSO-d_6, 353 K) δ 4.88 (d, J = 11.7 Hz, 1H), 4.83 (d, J = 11.7 Hz, 1H), 4.11 (q, J = 7.0 Hz, 2H), 3.62−3.44 (m, 2H), 3.23 (ddd, J = 3.5, 9.7, 13.8 Hz, 1H), 3.03 (dd, J = 8.6, 14.0 Hz, 1H), 2.63 (d, J = 16.0 Hz, 1H), 2.41 (d, J = 16.4 Hz, 1H), 1.87−1.70 (m, 2H), 1.50 (ddd, J = 4.1, 9.6, 14.0 Hz, 1H), 1.41 (s, 9H), 1.22 (t, J = 7.0 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6, 353 K) δ 170.1, 153.6, 80.1, 78.4, 59.6, 44.9, 38.6, 38.3, 34.1, 34.0, 29.8, 27.7, 13.5, 12.1. HRMS (m/z): calc. for $C_{16}H_{28}N_2O_6$ [M + Na]$^+$: 367.1840; found: 367.1838.

***tert*-Butyl *trans*-4-(2-Hydroxyethyl)-3-methyl-4-(nitromethyl)piperidine-1-carboxylate (7b).** A round-bottom flask was charged with *tert*-butyl *trans*-4-(2-ethoxy-2-oxoethyl)-3-methyl-4-(nitromethyl)piperidine-1-carboxylate (3.01 g, 8.74 mmol) and THF (15 mL) and then cooled to 0 °C. Lithium borohydride (2 M in THF, 11.5 mL, 23 mmol) was added dropwise, followed by methanol (2.0 mL, 49 mmol). The reaction was stirred at 0 °C for 15 min. The ice batch was removed, and the reaction was stirred for 1.5 h at rt. The reaction was then quenched with 1 M NaOH solution and diluted with ethyl acetate. The layers were separated, the organic layer was saved, and the aqueous was extracted with ethyl acetate (×3) and then washed with water (×2). The aqueous layer was concentrated in vacuo and stirred with ethyl acetate for 15 h. The aqueous layer was then stirred with 10% methanol in methylene chloride for 25 min, and the layers were separated. The combined organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo. Flash column chromatography (0% to 100% ethyl acetate/heptane) was then used to provide 1.21 g (46% yield) of the title compound (oil) as a single diastereomer. NMR studies show the 4-nitromethyl and 3-methyl groups with *trans* relative stereochemistry. See the SI for more details.

^{1}H NMR (400 MHz, DMSO-d_6, 353 K) δ 4.71 (d, J = 11.7 Hz, 1H), 4.66 (d, J = 11.7 Hz, 1H), 4.30 (t, J = 4.9 Hz, 1H), 3.64−3.48 (m, 4H), 3.12 (ddd, J = 3.1, 10.1, 13.6 Hz, 1H), 2.92 (dd, J = 9.4, 13.7 Hz, 1H), 1.81−1.69 (m, 2H), 1.67−1.55 (m, 1H), 1.49−1.42 (m, 2H), 1.40 (s, 9H), 0.88 (d, J = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6, 353 K) δ 153.7, 81.3, 78.3, 55.8, 45.1, 39.0, 38.3, 34.3, 31.2, 29.6, 27.7, 11.8. HRMS (m/z): calc. for $C_{14}H_{26}N_2O_5$ [M + Na]$^+$: 325.1734; found: 325.1726.

***tert*-Butyl *trans*-3-Methyl-4-(2-((methylsulfonyl)oxy)ethyl)-4-(nitromethyl)piperidine-1-carboxylate (8b).** A round-bottom flask was charged with *tert*-butyl *trans*-4-(2-hydroxyethyl)-3-methyl-4-(nitromethyl)piperidine-1-carboxylate (113 mg, 0.37 mmol), methylene chloride (5 mL), and trimethylamine (0.16 mL, 1.1 mmol) and then cooled to 0 °C. Methanesulfonyl chloride (58 μL, 0.75 mmol) was then added dropwise, and the reaction was allowed to stir for 1 h. The reaction was quenched with saturated aqueous sodium bicarbonate solution and stirred for 15 min at room temperature. The layers were separated, and the aqueous was extracted with methylene chloride (×3). The combined organic layers were further quenched with a small amount of methanol (to consume any unquenched methanesulfonyl chloride). The organic layers were then dried over sodium sulfate, filtered, and concentrated in vacuo. The crude material was then purified via flash column chromatography (20% to 80% ethyl acetate/heptane) to provide 126 mg (89% yield) of the title compound as an oil.

^{1}H NMR (400 MHz, DMSO-d_6, 353 K) δ 4.79 (d, J = 12.1 Hz, 1H), 4.67 (d, J = 12.1 Hz, 1H), 4.39−4.27 (m, 2H), 3.61−3.49 (m, 2H), 3.20 (ddd, J = 3.6, 9.6, 13.9 Hz, 1H), 3.16 (s, 3H), 3.01 (dd, J = 8.8, 13.9 Hz, 1H), 2.02 (td, J = 7.2, 14.9 Hz, 1H), 1.78 (td, J = 7.3, 14.7 Hz, 1H), 1.73−1.61 (m, 2H), 1.47 (ddd, J = 4.1, 9.6, 14.0 Hz, 1H), 1.41 (s, 9H), 0.90 (d, J = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6, 353 K) δ 153.7, 80.6, 78.3, 65.7, 44.9, 38.6, 38.2, 36.6, 34.3, 29.4, 28.5, 27.7,

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11.9. HRMS (m/z): calc. for $C_{15}H_{28}N_2O_7S$ $[M + Na]^+$: 403.1509; found: 403.1515.

2-Benzyl 8-(*tert*-Butyl) *trans*-6-Methyl-2,8-diazaspiro[4.5]decane-2,8-dicarboxylate (9b). A Parr reactor was charged *tert*-butyl *trans*-3-methyl-4-(2-((methylsulfonyl)oxy)ethyl)-4-(nitromethyl)piperidine-1-carboxylate (110 mg, 0.29 mmol) in 10 mL of ethanol. A small spatula tip of Raney Nickel 2800 slurry in water was then added, and the reactor was sealed, purged with nitrogen × 3, flushed with hydrogen × 3, and finally charged with 50 psi hydrogen. The reaction was stirred at rt for 48 h. The pressure was removed, and the reactor was flushed with nitrogen. The reaction was then filtered through a pad of Celite and washed with ethanol. The filtrate was then concentrated in vacuo to provide 101 mg (quant.) of a crude oil that was taken onto the next step without purification.

A round-bottom flask was charged with the crude oil, acetonitrile (2 mL), water (2 mL), and sodium carbonate (93 mg, 0.87 mmol) and then stirred vigorously. Benzyl chloroformate (83 μL, 0.58 mmol) was added dropwise, and the reaction was stirred for 5 h. The reaction was diluted with ethyl acetate and water. The layers were separated, and the aqueous was extracted with ethyl acetate × 2. The combined organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo. Flash column chromatography (20% to 75% ethyl acetate/heptane) was then used to provide 79 mg (70% yield) of the title compound as an oil.

^{1}H NMR (400 MHz, DMSO-d_6, 353 K) δ 7.44−7.23 (m, 5H), 5.08 (s, 2H), 3.47−3.30 (m, 4H), 3.29−3.12 (m, 4H), 1.78 (ddd, J = 8.6, 8.6, 12.9 Hz, 1H), 1.66−1.50 (m, 3H), 1.41 (s, 9H), 1.33 (ddd, J = 3.9, 6.7, 13.6 Hz, 1H), 0.87 (d, J = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6, 353 K) δ 153.8, 153.6, 136.9, 127.9, 127.3, 127.2, 126.9, 78.0, 65.4, 54.7, 46.8, 44.2, 42.9, 40.2, 36.0, 31.2, 27.7, 12.6. HRMS (m/z): calc. for $C_{22}H_{32}N_2O_4$ $[M + Na]^+$: 411.2254; found: 411.2253.

***tert*-Butyl 4-(1-Ethoxy-1-oxopropan-2-yl)-4-(nitromethyl)-piperidine-1-carboxylate (12a).** A 200 mL round-bottom flask was charged with the *tert*-butyl 4-(1-ethoxy-1-oxopropan-2-ylidene)-piperidine-1-carboxylate[18] (2.00 g, 7.06 mmol) and THF (20 mL). Nitromethane (1.6 mL, 28 mmol) and TBAF (1 M in THF, 11.4 mL, 11.4 mmol) were added via syringe. The reaction was heated to reflux temperature and stirred for 24 h. The reaction was cooled to room temperature, and the reaction was quenched with saturated aqueous ammonium chloride and stirred for 15 min, then diluted with water and ethyl acetate. The layers were separated, and the organic layer was washed with brine, dried over magnesium sulfate, filtered, and concentrated in vacuo. The crude material was subjected to flash chromatography (0% to 70% ethyl acetate/heptane) to provide 1.6 g (66% yield, 90% BRSM) of the title compound as a pale yellow oil and 540 mg (27%) of recovered starting material.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.74 (d, J = 11.3 Hz, 1H), 4.56 (d, J = 11.3 Hz, 1H), 4.10−4.18 (m, 2H), 3.60 (ddd, J = 4.3, 7.0, 14.1 Hz, 1H), 3.47−3.54 (m, 1H), 3.31−3.41 (m, 2H), 2.86 (q, J = 7.4 Hz, 1H), 1.69−1.82 (m, 2H), 1.53−1.67 (m, 2H), 1.43 (s, 9H), 1.25 (t, J = 7.2 Hz, 3H), 1.17 (d, J = 7.0 Hz, 3H). Contains 3 mol % heptanes as solvate unable to be removed. ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.0, 154.6, 79.8, 78.4, 60.7, 42.5, 38.8, 38.1, 29.8, 29.5, 28.3, 14.1, 11.6. HRMS (m/z): calc. for $C_{16}H_{28}N_2O_6$ $[M + Na]^+$: 367.1840; found: 367.1838.

***tert*-Butyl 4-(1-((Methylsulfonyl)oxy)propan-2-yl)-4-(nitromethyl)piperidine-1-carboxylate (13a).** Step 1: *tert*-butyl 4-(1-Hydroxypropan-2-yl)-4-(nitromethyl)piperidine-1-carboxylate.

A round-bottom flask was charged with *tert*-butyl 4-(1-ethoxy-1-oxopropan-2-yl)-4-(nitromethyl)piperidine-1-carboxylate (490 mg, 1.42 mmol) and methylene chloride (20 mL) and cooled to −78 °C. DIBAL (1.5 M in toluene, 2.37 mL, 3.56 mmol) was added dropwise, and the reaction was stirred for 5 h. An aliquot was removed and quenched and worked up with 0.5 M HCl solution. NMR indicated the presence of aldehyde and desired alcohol. Additional DIBAL (1.5 M in toluene, 0.50 mL, 0.75 mmol) was added slowly, and the reaction was stirred for an additional 1 h. The reaction was then quenched with Rochelle's salt solution and diluted with methylene chloride and stirred for 1 h until the layers turned clear and were free of emulsion. The layers were then separated, and the aqueous layer was extracted with methylene chloride (×3). The combined organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo. Flash column chromatography (20% to 100% ethyl acetate/heptane) was then used to provide 230 mg (54%) of *tert*-butyl 4-(1-hydroxypropan-2-yl)-4-(nitromethyl)piperidine-1-carboxylate as a thick colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.71 (d, J = 10.9 Hz, 1H), 4.56 (d, J = 11.3 Hz, 1H), 3.77 (dd, J = 4.7, 10.9 Hz, 1H), 3.60−3.68 (m, 3H), 3.24−3.34 (m, 2H), 1.97 (m, 1H), 1.76 (m, 2H), 1.70 (br. s, 1H), 1.60 (m, 2H), 1.46 (s, 9H), 1.02 (d, J = 7.0 Hz, 3H). Contains 4 mol % ethyl acetate and 7.5 mol % heptane as a solvate unable to be removed by concentration. ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.8, 79.8, 78.8, 63.7, 39.0, 38.64, 38.59, 30.3, 29.9, 28.3, 11.5. HRMS (m/z): calc. for $C_{14}H_{26}N_2O_5$ $[M + Na]^+$: 325.1734; found: 325.1734.

Step 2: *tert*-butyl 4-(1-((Methylsulfonyl)oxy)propan-2-yl)-4-(nitromethyl)piperidine-1-carboxylate.

A round-bottom flask was charged with *tert*-butyl 4-(1-hydroxypropan-2-yl)-4-(nitromethyl)piperidine-1-carboxylate (264 mg, 0.873 mmol), methylene chloride (10 mL), and trimethylamine (0.24 mL, 1.8 mL) and cooled to 0 °C. Methanesulfonyl chloride (74 μL, 0.96 mmol) was added dropwise. The reaction was then stirred at rt for 1 h. The reaction was quenched with aqueous sodium bicarbonate solution and stirred for 15 min at rt. The layers were separated, and the aqueous layer was extracted with methylene chloride (×3). The combined organic layers were further quenched with a small amount of methanol (to consume any unreacted MsCl), dried over sodium sulfate, filtered, and concentrated in vacuo to provide a yellow oil. The oil was sent through a small plug of silica eluted with ethyl acetate to provide 360 mg (quant.) of the title compound as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.58 (d, J = 11.7 Hz, 1H), 4.55 (d, J = 11.7 Hz, 1H), 4.33 (dd, J = 4.3, 10.1 Hz, 1H), 4.18 (dd, J = 6.6, 10.1 Hz, 1H), 3.79−3.69 (m, 2H), 3.24−3.13 (m, 2H), 3.05−3.02 (m, 3H), 2.15 (dt, J = 4.3, 6.8 Hz, 1H), 1.77−1.54 (m, 4H), 1.44 (s, 9H), 1.09 (d, J = 7.0 Hz, 3H). Contains 2.5 mol % CH_2Cl_2, 7.7 mol % EtOAc, 8.5 mol % heptane. ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.6, 80.0, 77.6, 70.1, 38.83 (br), 38.79, 37.5, 37.4, 30.3, 30.2, 28.3, 11.5. HRMS (m/z): calc. for $C_{15}H_{28}N_2O_7S$ $[M + Na]^+$: 403.1509; found: 403.1506.

2-Benzyl 8-(*tert*-Butyl) 4-Methyl-2,8-diazaspiro[4.5]decane-2,8-dicarboxylate (14a). A Parr reactor was charged with *tert*-butyl 4-(1-((methylsulfonyl)oxy)propan-2-yl)-4-(nitromethyl)piperidine-1-carboxylate (114 mg, 0.300 mmol) in 10 mL of ethanol. A small spatula tip of Raney Nickel 2800 (slurry in water) was then added, and the reactor was sealed, purged with nitrogen × 3, flushed with hydrogen × 3, and finally charged with 50 psi hydrogen. The reaction was stirred for 72 h at rt. The pressure was removed, and the reactor was flushed with nitrogen. The reaction was then filtered through a pad of Celite and washed with ethanol. The filtrate was concentrated in vacuo to provide 139 mg of a crude oil that was taken onto the next step without purification. MS (ES+): 255.1 (M + H).

A round-bottom flask was charged with the above crude oil, acetonitrile (2 mL), water (2 mL), and sodium carbonate (79 mg, 0.75 mmol) and then stirred vigorously. Benzyl chloroformate (64 μL, 0.45 mmol) was added dropwise, and the reaction was stirred for 5 h. The reaction was diluted with ethyl acetate and water. The layers were separated, and the aqueous was extracted with ethyl acetate × 2. The combined organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo. Flash column chromatography (20% to 75% ethyl acetate/heptane) was used to provide 104 mg (89% yield) of the title compound as an oil.

^{1}H NMR (400 MHz, DMSO-d_6, 353 K) δ 7.45−7.21 (m, 5H), 5.08 (s, 2H), 3.73 (br. d, J = 13.7 Hz, 2H), 3.57 (dd, J = 7.8, 10.1 Hz, 1H), 3.51 (d, J = 10.9 Hz, 1H), 3.13 (d, J = 10.9 Hz, 1H), 3.03−2.83 (m, 3H), 1.96 (sxt, J = 7.2 Hz, 1H), 1.54−1.45 (m, 1H), 1.41 (s, 9H), 1.38−1.23 (m, 3H), 0.88 (d, J = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6, 353 K) δ 153.7, 153.6, 136.9, 127.9, 127.2, 126.9, 78.1, 65.4, 52.9, 50.9, 40.7, 40.1, 33.2, 27.7, 27.2, 11.6. HRMS (m/z): calc. for $C_{22}H_{32}N_2O_4$ $[M + Na]^+$: 411.2254; found: 411.2250.

***tert*-Butyl 4-(2-Ethoxy-2-oxoethyl)-4-(1-nitroethyl)piperidine-1-carboxylate (12b).** *Small-Scale Procedure.* *tert*-Butyl 4-(2-ethoxy-2-oxoethylidene)piperidine-1-carboxylate (1.00 g, 3.71 mmol)

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was dissolved in THF (10 mL); then nitroethane (1.00 mL, 10.0 mmol) and TBAF (1 M in THF, 6.0 mL, 6.0 mmol) were added dropwise via syringe. The reaction was heated to reflux temperature and stirred for 2 h. The reaction was cooled to rt, and the reaction was quenched with saturated aqueous ammonium chloride solution and then diluted with water and ethyl acetate. The layers were separated, and the organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuo. Flash column chromatography (10% to 100% isopropanol/heptane) was used to provide 898 mg (70% yield) of the desired product as an oil.

^{1}H NMR (400 MHz, CDCl3) δ 5.05 (q, J = 6.8 Hz, 1H), 4.22−4.06 (m, 2H), 3.87 (d, J = 12.5 Hz, 1H), 3.80 (td, J = 4.3, 14.0 Hz, 1H), 3.11−3.01 (m, 2H), 2.59 (d, J = 15.6 Hz, 1H), 2.50 (d, J = 15.6 Hz, 1H), 1.61 (m, 4H), 1.51 (d, J = 7.0 Hz, 3H), 1.44 (s, 9H), 1.26 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, CDCl3) δ 170.5, 154.6, 87.7, 79.8, 60.7, 38.9, 37.9, 35.2, 30.2, 29.7, 28.3, 14.1, 13.5. HRMS (m/z): calc. for $C_{16}H_{28}N_2O_6$ [M + Na]$^+$: 367.1840; found: 367.1834.

Large-Scale Procedure. A 3 L, 3-neck, round-bottom flask was charged with *tert*-butyl 4-(2-ethoxy-2-oxoethylidene)piperidine-1-carboxylate (241.85 g, 897.93 mmol) and dissolved in THF (900 mL). Nitroethane (130 mL, 1800 mmol) was added, followed by TBAF (1 M in THF, 890 mL, 890 mmol) via addition funnel. The reaction was heated to 50 °C and stirred for 15 h. The reaction was cooled to rt, and the reaction was quenched with 10% aqueous ammonium chloride solution (1 L) and then diluted with ethyl acetate (1 L). The layers were separated, and the aqueous layer was extracted with ethyl acetate (1 L). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuo. ^{1}H NMR showed a substantial amount of tetrabutylammonium salts present. The crude oil was then diluted with *t*-butyl methyl ether, slurried, and transferred to a separatory funnel. A bottom, oily layer was removed, and the organic layer was saved. The oily layer was extracted with *t*-butyl methyl ether twice more using this process. The combined organic layers were then dried over sodium sulfate, filtered, and concentrated to provide 273.3 g (88% yield) of the desired product containing ∼7 mol % tetrabutyl ammonium salts. All other analytical information matched the reported data. This material was carried forward without further purification.

tert-Butyl 4-(2-((Methylsulfonyl)oxy)ethyl)-4-(1-nitroethyl)-piperidine-1-carboxylate (13b). *Small-Scale Procedure.* Step 1: *tert*-butyl 4-(2-hydroxyethyl)-4-(1-nitroethyl)piperidine-1-carboxylate.

A round-bottom flask was charged with *tert*-butyl 4-(2-ethoxy-2-oxoethyl)-4-(1-nitroethyl)piperidine-1-carboxylate (208 mg, 0.604 mmol) and diethyl ether (5 mL). The reaction was cooled to 0 °C, lithium borohydride (2.0 M in THF, 0.80 mL, 1.6 mmol) was added, and the reaction was stirred for 30 min before being warmed to rt. The reaction was then stirred for 15 h at rt, and the reaction was quenched with aqueous 1 M NaOH solution and stirred for 10 min. The reaction was then diluted with ethyl acetate, and the layers were separated. The aqueous was extracted with ethyl acetate × 3, and the combined organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo. Flash column chromatography (20% to 100% ethyl acetate/heptane) was then used to provide 134 mg (73%) of *tert*-butyl 4-(2-hydroxyethyl)-4-(1-nitroethyl)piperidine-1-carboxylate as a clear, colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.88 (q, J = 7.0 Hz, 1H), 3.86−3.66 (m, 4H), 3.14 (ddd, J = 4.1, 9.8, 13.9 Hz, 2H), 1.89−1.72 (m, 2H), 1.86 (s, 1H), 1.67−1.51 (m, 4H), 1.50 (d, J = 7.2 Hz, 3H), 1.44 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.8, 88.3, 79.8, 58.0, 39.0, 37.8, 33.2, 30.2, 30.0, 28.4, 13.6. HRMS (m/z): calc. for $C_{14}H_{26}N_2O_5$ [M + Na]$^+$: 325.1734; found: 325.1729.

Step 2: *tert*-butyl 4-(2-((methylsulfonyl)oxy)ethyl)-4-(1-nitroethyl)-piperidine-1-carboxylate.

A round-bottom flask was charged with *tert*-butyl 4-(2-hydroxyethyl)-4-(1-nitroethyl)piperidine-1-carboxylate (134 mg, 0.443 mmol) and methylene chloride (5 mL). Triethylamine (0.12 mL, 0.88 mmol) was added, followed by methanesulfonyl chloride (41 μL, 0.53 mmol). The reaction was stirred for 15 min and then quenched with saturated sodium bicarbonate and extracted with methylene chloride. The combined organics were dried over sodium sulfate, filtered, and concentrated in vacuo. Flash chromatography (10% to 75% ethyl acetate/heptane) was used to provide 138 mg (82%) of the title compound as an oil.

^{1}H NMR (400 MHz, DMSO-d_6) δ 5.01 (q, J = 6.6 Hz, 1H), 4.30 (t, J = 7.2 Hz, 2H), 3.62 (td, J = 4.7, 13.7 Hz, 1H), 3.53 (td, J = 4.6, 13.9 Hz, 1H), 3.20 (s, 3H), 3.24−3.11 (br. s, 2H), 2.02−1.91 (m, 1H), 1.91−1.78 (m, 1H), 1.52−1.35 (m, 4H), 1.43 (d, J = 6.6 Hz, 3H), 1.39 (s, 9H). ^{13}C NMR (101 MHz, DMSO) δ 153.9, 87.4, 78.7, 66.3, 38.3, 37.3, 36.6, 29.8, 29.6, 28.0, 13.2. HRMS (m/z): calc. for $C_{15}H_{28}N_2O_7S$ [M + Na]$^+$: 403.1509; found: 403.1504.

Large-Scale Procedure. Step 1: *tert*-butyl 4-(2-hydroxyethyl)-4-(1-nitroethyl)piperidine-1-carboxylate.

A round-bottom flask was charged with *tert*-butyl 4-(2-ethoxy-2-oxoethyl)-4-(1-nitroethyl)piperidine-1-carboxylate (140.9 g, 409.1 mmol) and THF (550 mL). The reaction was cooled to 0 °C, and lithium borohydride (2.0 M in THF, 245 mL, 491 mmol) was added via addition funnel over 10 min. Methanol (20.1 mL, 491 mmol) was added dropwise via addition funnel over 1 h. During addition, an exotherm was noted as the temperature rose to 20 °C. The drop rate was adjusted to keep the temperature < 20 °C for the remainder of the addition. The ice bath was removed, and the reaction was warmed to rt and then stirred for 15 h. Starting material was still present, so the reaction was cooled back to 0 °C and additional lithium borohydride (2 M in THF, 41 mL, 82 mmol) was added dropwise, followed by additional methanol (3.31 mL, 82.0 mmol). The reaction was warmed to rt and stirred for an additional 5 h to drive the reaction to completion. The reaction was quenched by carefully pouring onto 1.5 L of ice water with vigorous stirring. The mixture was stirred for 1 h. Ethyl acetate (1 L) was added to extract, and the layers were separated. The aqueous layer was extracted with ethyl acetate (500 mL). The combined organic layers were washed with half-saturated ammonium chloride solution (600 mL), then brine (500 mL), dried over sodium sulfate, filtered, and concentrated in vacuo. Next, 500 mL of methanol was added and the mixture was concentrated in vacuo to remove any boron-containing impurities to provide 111.2 g (90%) of *tert*-butyl 4-(2-hydroxyethyl)-4-(1-nitroethyl)piperidine-1-carboxylate as an oil that was taken on forward without further purification. The major component of the mixture matched the previously reported analytical data.

Step 2: *tert*-butyl 4-(2-((methylsulfonyl)oxy)ethyl)-4-(1-nitroethyl)-piperidine-1-carboxylate.

A round-bottom flask was charged with *tert*-butyl 4-(2-hydroxyethyl)-4-(1-nitroethyl)piperidine-1-carboxylate (175.6 g, 580.7 mmol) and methylene chloride (1.15 L). Triethylamine (161 mL, 1.16 mol) was added, and the reaction was cooled to 0 °C. Methanesulfonyl chloride (46.2 mL, 592 mmol) was added dropwise, and the reaction was stirred for 30 min. The reaction was quenched by pouring onto 1 L of ice and saturated sodium bicarbonate solution; then the mixture was stirred vigorously for 15 min. The layers were separated, and the aqueous was extracted with methylene chloride. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated. 1.4 L of ethanol was then added, and the material slowly dissolved with stirring at rt. The mixture was then stirred for 15 h. During this time, white solid material had formed, which was filtered off to provide 88.75 g of the desired product with high purity. The mother liquor was then concentrated to $^1/_2$ the volume and stirred for 2 days. A second crop of solid formed, which was collected and dried to provide an additional 51.8 g of the desired product with high purity. The process was repeated once more to form a third crop that was collected and dried to provide 9.4 g of the title compound. The total yield was 150 g (68%) of the title compound as a white solid that matched the previously reported analytical data.

2-Benzyl 8-(*tert*-Butyl) 1-Methyl-2,8-diazaspiro[4.5]decane-2,8-dicarboxylate (14b). A Parr reactor was charged with *tert*-butyl 4-(2-((methylsulfonyl)oxy)ethyl)-4-(1-nitroethyl)piperidine-1-carboxylate (217 mg, 0.570 mmol) in 10 mL of ethanol. A small spatula tip of Raney Nickel 2800 (slurry in water) was added, and the reactor was sealed, purged with nitrogen × 3, flushed with hydrogen × 3, and finally charged with 50 psi hydrogen. The reaction was stirred for 72 h at rt. The pressure was removed, and the reactor was flushed with

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nitrogen. The reaction was filtered through a pad of Celite and washed with ethanol. The filtrate was then concentrated in vacuo to provide 145 mg of a crude oil that was taken onto the next step without purification. MS (AP+): 255.2 (M + H).

A round-bottom flask was charged with the crude oil, acetonitrile (2 mL), water (2 mL), and sodium carbonate (153 mg, 1.42 mmol) and then stirred vigorously. Benzyl chloroformate (0.12 mL, 0.86 mmol) was added dropwise, and the reaction was stirred for 5 h. The reaction was diluted with ethyl acetate and water. The layers were separated, and the aqueous was extracted with ethyl acetate × 2. The combined organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo. Flash column chromatography (20% to 75% ethyl acetate/heptane) was then used to provide 134 mg (61% yield) of the desired product as an oil.

^{1}H NMR (400 MHz, DMSO-d_6, 353 K) δ 7.41−7.26 (m, 5H), 5.10 (d, J = 12.7 Hz, 1H), 5.06 (d, J = 12.7 Hz, 1H), 3.65 (q, J = 6.5 Hz, 1H), 3.50−3.39 (m, 2H), 3.39−3.32 (m, 2H), 3.26 (ddd, J = 4.7, 8.3, 13.6 Hz, 1H), 3.16 (ddd, J = 3.5, 9.1, 13.2 Hz, 1H), 1.84 (ddd, J = 3.5, 6.4, 13.3 Hz, 1H), 1.79−1.68 (m, 1H), 1.48 (ddd, J = 3.5, 9.0, 13.3 Hz, 1H), 1.41 (s, 9H), 1.39−1.32 (m, 3H), 1.04 (d, J = 6.2 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6, 353 K) δ 153.62, 153.62, 136.9, 127.9, 127.2, 126.9, 78.1, 65.3, 59.6, 42.7, 41.9, 40.5, 39.9, 33.5, 30.8, 27.8, 14.6. HRMS (m/z): calc. for $C_{22}H_{32}N_2O_4$ [M + Na]$^+$: 411.2254; found: 411.2256.

tert-Butyl 4-Cyano-4-(2-hydroxypropyl)piperidine-1-carboxylate (16). A round-bottom flask was charged with with diisopropylamine (0.67 mL, 4.8 mmol) and THF (6 mL) and then cooled to −78 °C. _n_-Butyllithium (2.5 M in hexanes, 1.9 mL, 4.8 mmol) was added dropwise, and the mixture warmed to 0 °C for 10 min, then cooled back to −78 °C. A solution of Boc-4-cyanopiperidine (1.00 g, 4.75 mmol) in tetrahydrofuran (10 mL) was added dropwise to the formed lithium diisopropylamide solution. The reaction was stirred at −78 °C for 10 min, then at 0 °C for 15 min. The reaction was cooled back to −78 °C, and propylene oxide (0.33 mL, 4.8 mmol) was added. The reaction then slowly warmed to rt and was stirred for 2 h. The reaction was then cooled to −78 °C, and solid ammonium chloride was added. The mixture was stirred for 30 min at −78 °C; then 2 M HCl (1.5 mL) was added and the reaction warmed to rt. Ethyl acetate was added, and the layers were separated. The aqueous layer was extracted with ethyl acetate × 2. The combined organic layers were washed with water, dried over sodium sulfate, filtered, and concentrated in vacuo. Flash column chromatography (10% to 70% ethyl acetate/heptane) was then used to provide 1.17 g (92% yield) of the title compound as a solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.26−4.17 (br. m, 1H), 4.10 (br. s, 2H), 3.21−2.91 (br. m, 2H), 2.16 (br. d, J = 13.3 Hz, 1H), 1.93 (br. d, J = 13.3 Hz, 1H), 1.86−1.59 (m, 3H), 1.58−1.36 (m, 11H), 1.28 (br. d, J = 5.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.5, 122.5, 80.0, 65.0, 48.1, 40.8, 36.5, 35.4, 35.0, 28.4, 25.2. HRMS (m/z): calc. for $C_{14}H_{24}N_2O_3$ [M + Na]$^+$: 291.1679; found: 291.1675.

tert-Butyl 4-Cyano-4-(2-((methylsulfonyl)oxy)propyl)piperidine-1-carboxylate (17). A round-bottom flask was charged with _tert_-butyl 4-cyano-4-(2-hydroxypropyl)piperidine-1-carboxylate (589 mg, 2.19 mmol) and methylene chloride (20 mL) and then cooled to 0 °C. Triethylamine (0.61 mL, 4.4 mmol) and 4-(dimethylamino)-pyridine (19 mg, 0.15 mmol) were added, followed by methanesulfonyl chloride (0.24 mL, 3.1 mmol). The reaction was stirred at 0 °C for 1 h and then quenched with saturated sodium bicarbonate solution and diluted with methylene chloride. The layers were separated, and the aqueous was extracted with methylene chloride. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuo. Flash column chromatography (10% to 50% ethyl acetate/heptane) was used to isolate 695 mg (91% yield) of the title compound as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.13 (dqd, J = 3.1, 6.2, 9.4 Hz, 1H), 4.15 (br. m. 2H), 3.74 (s, 3H), 3.11−3.01 (m, 2H), 2.15 (dd, 14.8, 9.4 Hz, 1H), 2.09 (dq, J = 13.3, 2.3 Hz, 1H), 1.99 (dq, J = 13.7, 2.3 Hz, 1H), 1.71−1.65 (m, 1H), 1.55 (d, J = 6.2 Hz, 3H), 1.52−1.38 (m, 2H), 1.46 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.3, 121.6, 80.2, 73.3, 46.1, 40.4, 38.9, 35.7, 35.3, 33.9, 28.4, 22.5. HRMS (m/z): calc. for $C_{15}H_{26}N_2O_5S$ [M + Na]$^+$: 369.1455; found: 369.1453.

2-Benzyl 8-(_tert_-Butyl) 3-Methyl-2,8-diazaspiro[4.5]decane-2,8-dicarboxylate (18). A round-bottom flask was charged with the _tert_-butyl 4-cyano-4-(2-((methylsulfonyl)oxy)propyl)piperidine-1-carboxylate (300 mg, 0.87 mmol) and THF (5 mL) and then cooled to 0 °C. Lithium aluminum hydride powder (72 mg, 1.9 mmol) was added. The mixture was stirred at 0 °C for 15 min, then warmed to 1.5 h, then quenched with sequential additions of 75 μL of water, 75 μL of 15% NaOH, and 225 μL of water, and then stirred 10 min. Sodium sulfate was added, and the mixture was stirred for 20 min, filtered through Celite, and washed sequentially with THF, then ethyl acetate. The filtrate was concentrated in vacuo to provide 238 mg (quant.) of the title compound as an oil that was brought forward to the next step without further purification. MS(ES+): 255.3 (M + H).

A round-bottom flask was charged with the crude oil, acetonitrile (6 mL), water (5.2 mL), and sodium carbonate (278 mg, 2.60 mmol) and then stirred vigorously. Benzyl chloroformate (0.25 mL, 1.7 mmol) was added dropwise, and the reaction was stirred for 5 h. The reaction was then diluted with ethyl acetate and water. The layers were separated, and the aqueous was extracted with ethyl acetate × 2. The combined organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo. Flash column chromatography (20% to 75% ethyl acetate/heptane) was used to provide 159 mg (47% over two steps) of the title compound as an oil.

^{1}H NMR (400 MHz, DMSO-d_6, 353 K) δ 7.45−7.23 (m, 5H), 5.12 (d, J = 13.1 Hz, 1H), 5.05 (d, J = 13.1 Hz, 1H), 3.93−3.80 (m, 1H), 3.52 (dd, J = 1.2, 10.9 Hz, 1H), 3.42−3.19 (m, 4H), 3.09−3.06 (m, 1H), 2.11 (ddd, J = 1.2, 7.4, 12.9 Hz, 1H), 1.56−1.44 (m, 2H), 1.41 (s, 9H), 1.37−1.29 (m, 3H), 1.23 (d, J = 5.9 Hz, 3H). ^{13}C NMR (400 MHz, DMSO-d_6, 353 K) δ 153.9, 153.6, 136.9, 127.9, 127.2, 126.9, 78.1, 65.4, 55.4, 51.4, 43.6, 40.8, 40.2, 34.4, 33.3, 27.7, 20.5. HRMS (m/z): calc. for $C_{22}H_{32}N_2O_4$ [M + Na]$^+$: 411.2254; found: 411.2253.

Mono((_S_)-8-(_tert_-butoxycarbonyl)-1-methyl-2,8-diazaspiro-[4.5]decan-2-ium) Mono((2_R_,3_S_)-2,3-bis((4-methylbenzoyl)-oxy)succinate) (20). A pressure reactor was charged with _tert_-butyl 4-(2-((methylsulfonyl)oxy)ethyl)-4-(1-nitroethyl)piperidine-1-carboxylate (50 g, 131 mmol) and 400 mL of ethanol. Raney Nickel was added (slurry in water, not quantified), and the reaction was pressurized to 50 psi hydrogen and then stirred for 24 h. The reaction was filtered and concentrated in vacuo. The residue was dissolved in dichloromethane and treated with 10% sodium carbonate solution and then shaken in a separatory funnel. The layers were separated, and the aqueous was extracted with dichloromethane (×3). The combined organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo to provide 24 g of crude oil. The oil was dissolved in 95% ethanol (1 L) and treated with (−)-_O,O′_-di-_p_-toluoyl-L-tartaric acid (36.45 g, 94.34 mmol) with stirring. A small seed crystal was added (obtained by performing the resolution on a small scale and applying heating and cooling cycles), and white solids slowly crystallized. An additional 500 mL of 95% ethanol was added to aid in stirring. The slurry was stirred for 3 days, filtered, and washed with a small amount of cold 95% ethanol. The solids were dried on the filter and in vacuo to provide **20** (18 g, 28 mmol, 21% yield, two steps) with 84.7% ee. This batch was combined with 24 g of **20** with 87.6% ee (obtained from a less optimized process) and subjected to a recrystallization by dissolving in ethanol with heating to 75 °C, cooling to rt, stirring for 4 days, filtering, and drying to obtain **20** (24 g, 57% recovery) with 98.9% ee. A single crystal of sufficient quality was subsequently grown by slow evaporation of a mixture of **20** (20 mg) in methanol (1 mL) over 3 days and submitted for X-ray single-crystal diffraction analysis.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.82−8.47 (br. m, 2H), 7.85 (d, J = 8.2 Hz, 4H), 7.32 (d, J = 8.2 Hz, 4H), 5.62 (s, 2H), 3.73 (br. d, J = 12.5 Hz, 2H), 3.11 (t, J = 7.8 Hz, 2H), 3.02 (q, J = 6.9 Hz, 1H), 2.79 (br. s, 2H), 2.37 (s, 6H), 2.00 (td, J = 6.8, 13.4 Hz, 1H), 1.64−1.51 (m, 1H), 1.39 (s, 9H), 1.33−1.22 (m, 2H), 1.20−1.09 (m, 2H), 0.99 (d, J = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.2, 164.8, 153.8, 143.7, 129.3, 129.2, 126.9, 78.6, 72.1, 61.6, 42.3, 41.0, 40.1, 33.1,

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31.0, 28.0, 27.7, 21.2, 11.4. mp = 172.4−173.2 °C. $[\alpha]_D^{20}$ −97.7 (*c* 0.69, CH_3OH). 98.86% ee (see the SI for SFC trace).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02890.

NMR spectra, enantioselectivity assay, and crystallographic data (PDF)

Crystallographic data for **20** (CIF)

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Notes

The authors declare no competing financial interest.

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