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Stereoselective Synthesis of Spiropiperidines as BACE-1 Aspartyl Protease Inhibitors via Late Stage *N*-Arylation of a 1,8-Diazaspiro[4.5]dec-3-en-2-one Pharmacophore

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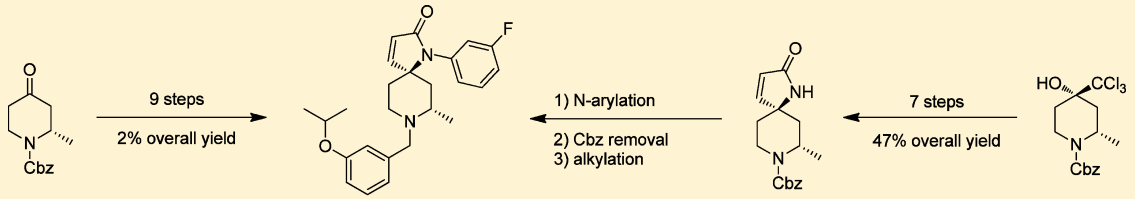
Supporting Information



ABSTRACT: A stereoselective synthesis of spiropiperidine compounds, exemplified by compound **1**, was developed, which was based upon the late stage *N*-arylation of a 1,8-diazaspiro[4.5]dec-3-en-2-one pharmacophore. Previously, compound **1** was prepared in low overall yield from piperidinone **2** via the Strecker reaction. A new route was developed, which employed the stereospecific Corey–Link reaction of an enantiomerically pure trichloromethylcarbinol to give a template compound amenable to late stage *N*-arylation.

INTRODUCTION

Spiropiperidine compounds have found broad utility in a wide variety of therapeutic programs as chemokine cell surface receptor antagonists,[1] calcium channel blockers,[2] and G-protein coupled receptor ligands[3] and have also been identified as inhibitors for aspartyl protease enzymes such as Renin.[4] During the course of our efforts to identify a novel series of β-site amyloid precursor protein cleaving enzyme (BACE-1) inhibitors, compound **1** was identified as a lead compound with desirable properties.[5] One of the strategies for improving the overall biological profile of the compound involved maintaining the 1,8-diazaspiro[4.5]dec-3-en-2-one pharmacophore while varying the surrounding substituents. Since compound **1** contained a fairly lipophilic 3-fluorophenyl moiety, a systematic investigation was carried out to identify aryl and heteroaryl replacements that would improve its physicochemical properties. However, this proved to be a challenging endeavor as the initial route used to prepare compound **1** was low yielding and not easily amenable to variation within the *N*-aryl region.

The initial route used to prepare compound **1** is shown in Scheme 1. Treatment of optically active piperidinone **2**[6] with 3-fluoroaniline and zinc cyanide afforded the desired Strecker product in 78% yield as a 40:60 mixture of diastereomers **3a** and **3b**, respectively.[7] The desired diasteromer **3b** was separated from the mixture via chiral HPLC. Acylation of the secondary amine of **3b** was carried out with ethyl malonyl chloride in the presence of the hindered base 2,6-lutidine to afford the desired malonamide **4** in modest yield. Subsequent treatment of **4** with sodium ethoxide in ethanol resulted in intramolecular cyclization to afford the desired enamine **5** in essentially quantitative yield. Enamine **5** was then refluxed in aqueous 6 N HCl to effect both the saponification/decarboxylation of the ethyl ester and the hydrolysis of the enamine to the corresponding ketone. Under these strongly acidic conditions, the Cbz group was cleaved, and therefore the piperidine nitrogen was reprotected with Cbz-Cl to afford the desired β-ketoamide **6** in low yield (23%) over two steps. Reduction of the ketone in **6** with sodium borohydride provided a mixture of alcohols (**7**) in essentially quantitative yield. Subsequent elimination of the hydroxyl group with thionyl chloride in pyridine followed by removal of the Cbz protecting group with aqueous acid (6 N HCl/MeOH) furnished piperidine **9**. A final alkylation of **9** with 1-bromomethyl-3-isopropoxy benzene provided compound **1**.

Variation of the *N*-aryl region of **1** using this route was cumbersome because of the fact that the aryl moiety is introduced in the first step as an aniline via the Strecker reaction in a nonstereoselective fashion. Additionally, although a large number of anilines are commercially available, many of the electron deficient ones (e.g., aminopyridines) would not react well, if at all, under the Strecker conditions. Moreover, the frequent use of zinc cyanide, the potential need to use chiral

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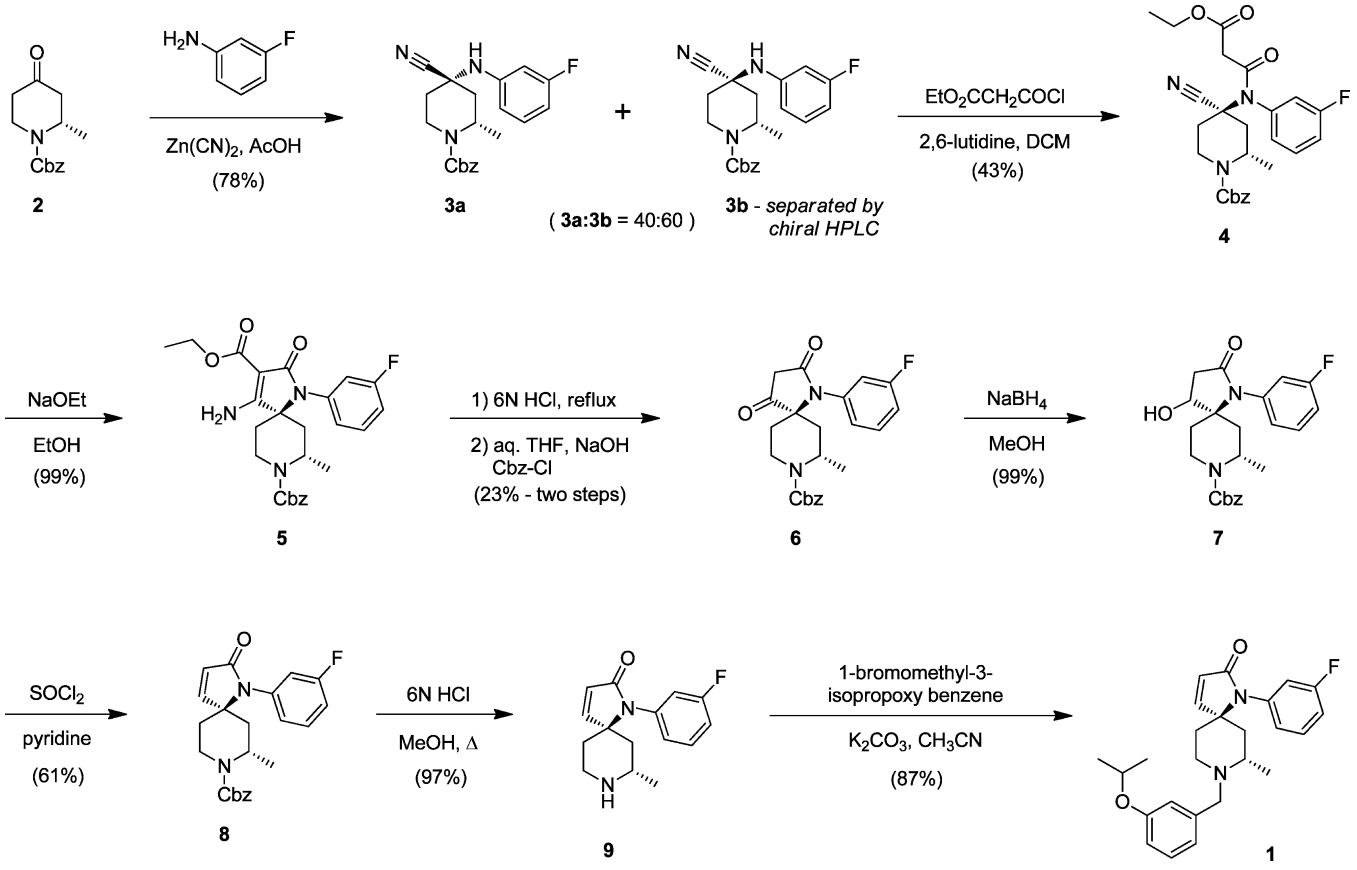
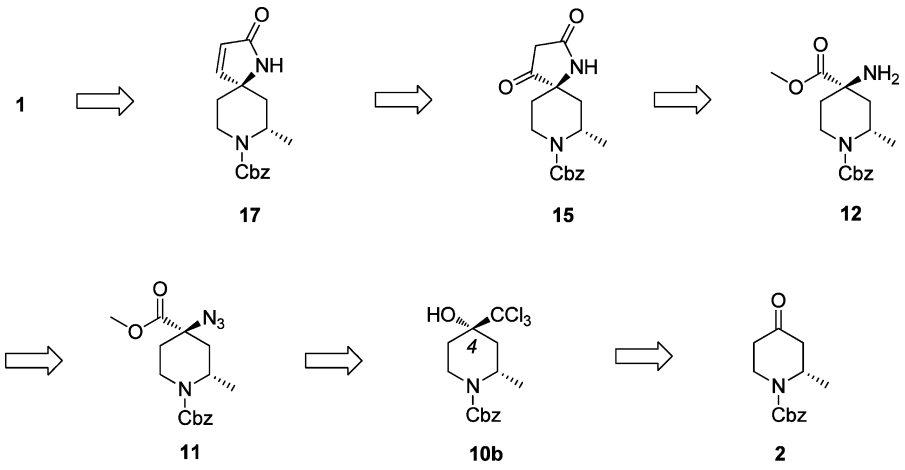
Scheme 1. Original Synthesis of Compound 1 via the Strecker Route



Scheme 2. Retrosynthetic Approach for a Late Stage *N*-Arylation Strategy



chromatography after each Strecker condensation, and the overall length of the sequence (nine steps from piperidinone **2**, 2% overall yield in the case of 3-fluoroaniline) were not conducive to the rapid exploration of the *N*-aryl region. In order to facilitate the exploration of this region, we sought an alternate route that would allow variation of the aryl moiety much later in the sequence via the metal mediated cross coupling of an unsubstituted lactam with aryl halides.

RESULTS AND DISCUSSION

The retrosynthetic approach for this new route is outlined in Scheme 2. We envisioned access to a variety of compounds related to **1** via the late stage metal mediated *N*-arylation of spirolactam **17** with various aryl or heteroaryl halides. Spirolactam **17** in turn can be accessed from *β*-ketolactam **15** using standard reduction and elimination procedures. *β*-Ketolactam **15** can be prepared from amino-ester **12** via acylation followed by ketolactam formation, similar to the sequence of operations previously described in Scheme 1.

In order to access the key amino-ester **12** as a single diastereomer, we anticipated that C(4) inversion via a modified Corey–Link reaction using enantiomerically pure trichloromethylcarbinol **10b** followed by azide reduction would provide the desired compound with the correct absolute stereochemistry.[8]

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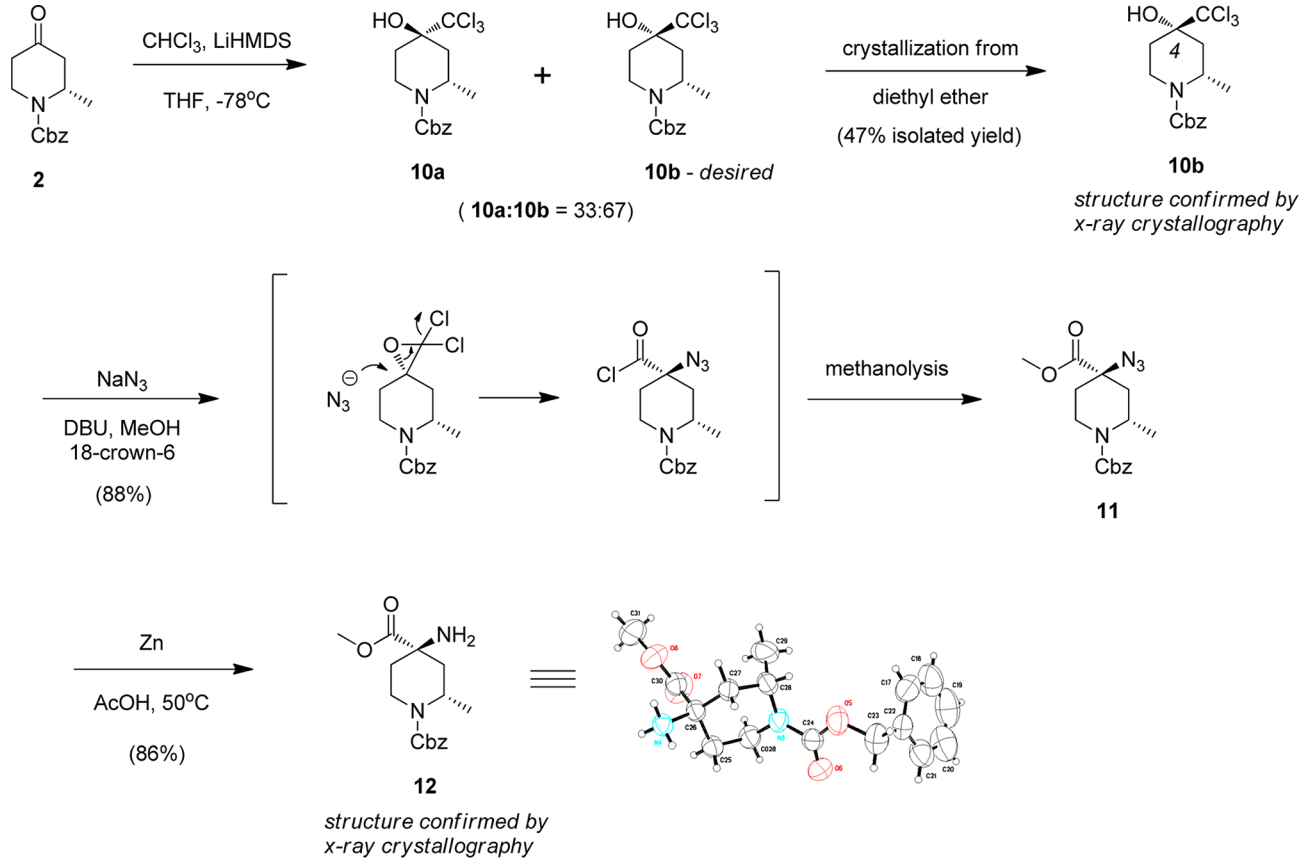
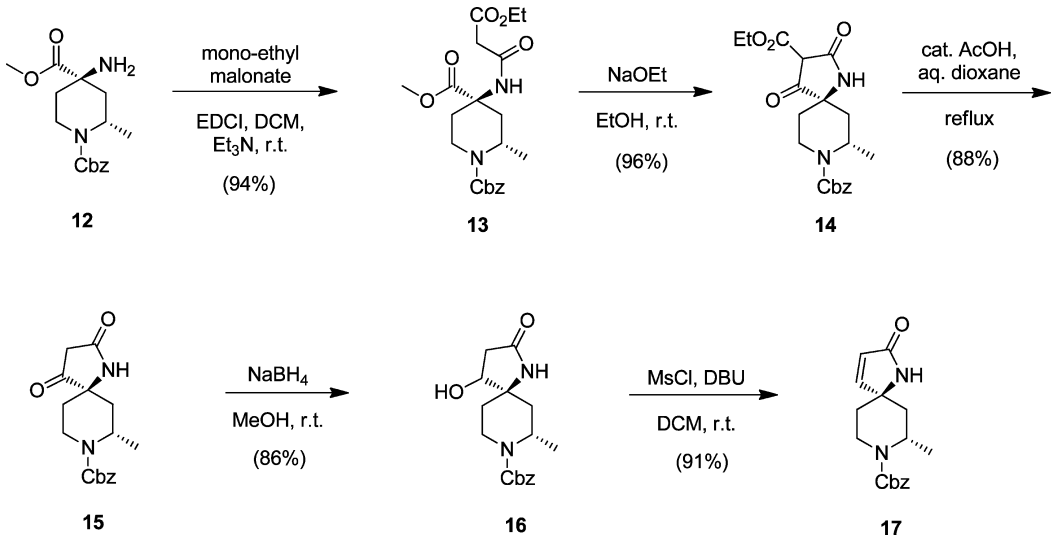
Scheme 3. Stereoselective Synthesis of Amino-Ester 12 via the Corey−Link Reaction



Scheme 4. Completion of the Synthesis of the Spirolactam Pharmacophore 17



Trichloromethylcarbinol **10b** can in turn be prepared via the base promoted addition of chloroform to optically active piperidinone **2**.[9]

In the forward sense, the new approach began with the synthesis of amino-ester **12** (Scheme 3). Treatment of piperidinone **2** with in situ generated trichloromethyl lithium at −78 °C provided trichloromethylcarbinols **10a** and **10b** as a 33:67 mixture of diastereomers, with the bulky trichloromethyl anion favoring approach from the side opposite the methyl group. We were pleased to find that the desired major diastereomer (**10b**) could be readily separated from the mixture in 47% yield by crystallization from diethyl ether, thus avoiding the use of chiral chromatography for purification. The absolute stereochemistry of **10b** was subsequently confirmed via single crystal X-ray crystallography. Treatment of trichloromethylcarbinol **10b** with sodium azide in the presence of DBU and methanol resulted in a key C(4) stereocenter inversion and provided **11** in 88% yield as a single diastereomer. The reaction is likely to proceed via an in situ generated gem-dichloroepoxide intermediate followed by regioselective epox-

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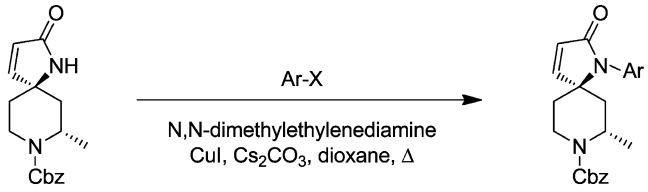
ide opening at C(4) with an azide anion.[8,10] Gem-dichloroepoxide intermediates have been reported in the literature, and have even been isolated in some cases.[11] Subsequent reduction of the crude azide-ester **11** with zinc metal in acetic acid furnished the desired amino-ester **12** in 86% yield. Single crystal X-ray crystallographic analysis of the mono-HCl salt of **12** verified that complete inversion had taken place during the previous reaction.

Scheme 4 outlines the final elaboration of amino-ester **12** to the key spirolactam pharmacophore **17**. Acylation of the amino group in **12** with monoethyl malonate using the coupling reagent EDCI afforded malonamide **13** in essentially quantitative yield. Subsequent exposure of crude **13** to a 21% solution of sodium ethoxide in EtOH resulted in a rapid intramolecular Dieckmann cyclization to afford intermediate **14**, again in near quantitative yield. Crude **14** was subsequently refluxed in aqueous dioxane to effect a one pot hydrolysis–decarboxylation sequence to afford the desired β-ketoamide **15** in 88% isolated yield. It should be noted that slightly acidic conditions are essential for the decarboxylation step; when the reaction was carried out under alkaline conditions (e.g., aqueous NaOH or LiOH), decarboxylation did not occur to any appreciable extent, presumably due to the rapid deprotonation of the starting material to give an inert, stabilized enolate anion of **14**. It is worth mentioning that this was the only step in the sequence from **2** to **14** where chromatographic purification was employed. Subsequent reduction of the ketone in **15** with $NaBH_4$ afforded the corresponding β-hydroxy amide **16** as a mixture of diastereomers in 88% yield. Finally, elimination of the resulting alcohol with methanesulfonyl chloride in the presence of DBU provided the desired spirolactam template compound **17** in 91% yield. This route to the spirolactam pharmacophore **17** (Schemes 3 and 4) was highly scalable, and the material was successfully prepared in batches of up to 150 g.

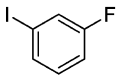
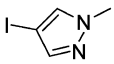
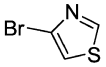
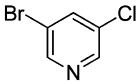
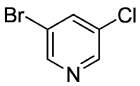
The *N*-arylation of lactams using Goldberg conditions[12] is well precedented in the literature, and the unsubstituted spirolactam **17** was found to successfully couple with a variety of aryl and heteroaryl halides in the presence of CuI and *N*,*N*′-dimethylaminoethylene diamine (Scheme 5).

It should be noted that a study of the Goldberg reaction by Buchwald et al.[13] has shown that increasing the amount of diamine ligand relative to copper improves the efficiency of the coupling, and this was found to be the case in example **22**. When spirolactam **17** was coupled with 3-bromo-5-chloropyridine using 1:1 CuI:DMEDA, the desired product was only obtained in 14% yield. However, when the ratio of the diamine ligand to copper was increased to 14:1, the yield of the desired product increased to 70%. Using these improved conditions, 3-fluoro-1-iodobenzene was successfully coupled with **17** in 84% yield to afford **8**, which was the same intermediate previously prepared via the original Strecker route (Scheme 1). The reaction was similarly successful with a variety of other heteroaryl iodides and bromides, allowing for the installation of pyridine, pyrazine, pyrazole, and thiazole moieties (entries **18**–**22**). In the previous route, as shown in Scheme 1, the preparation of these compounds would require the condensation of the corresponding heteroaryl amines with piperidinone **2** in a Strecker reaction, and it is likely that these reactions would be difficult to carry out because of the highly electron deficient nature of the requisite amines.

Scheme 5. Copper Mediated *N*-Arylation of Spirolactam 17 with Aryl Halides[b]



17

Product	Aryl Halide	Time	Yield
8		2 h	84%
18		4 h	72%
19		4 h	69%
20		18 h	63%
21		18 h	71%
22		18 h	70%
22[a]		18 h	14%

[a]Ratio of CuI:DMEDA was changed from 1:14 to 1:1. [b]Conditions: 1.0 equiv of **17**, 2.0 equiv of Ar–X, 0.5 equiv of CuI, 7.0 equiv of *N*,*N*′-dimethylaminoethylene diamine (DMEDA), 3.0 equiv of Cs_2CO_3, dioxane (5 mL/mmol), heated at 90 °C for the indicated times.

■ CONCLUSION

A modified Corey–Link route to a series of spiropiperidine BACE-1 inhibitors (exemplified by **1**) was developed, which offered several advantages when compared to the synthesis of these compounds via the original Strecker route: the *N*-aryl moiety can be installed late in the sequence allowing for rapid variation, the overall yield and scalability were improved, and almost all of the intermediates could be purified via crystallization or an aqueous workup; only one chromatographic purification was necessary in the 8 step sequence from piperidinone **2** to spirolactam **17**. Moreover, the modified route no longer required the use of zinc cyanide because the Strecker reaction had been replaced by the Corey–Link reaction for the construction of the spiroamine center. Also, an early crystallization to give **10b** followed by a series of stereospecific transformations allowed for the preparation of spirolactam **17** as a single diastereomer, thereby eliminating the potential need to use chiral HPLC for stereoisomer separation. Finally, a late

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stage copper mediated Goldberg reaction using spirolactam **17** allowed for the facile installation of a variety of aryl and heteroaryl moieties, greatly facilitating the exploration of the *N*-aryl region of compound **1**.

EXPERIMENTAL SECTION

General Experimental Methods. All reactions were carried out under a nitrogen atmosphere with commercially purchased reagents and anhydrous solvents, unless otherwise noted. Chemical shifts were recorded in ppm relative to solvent with multiplicities given as s (singlet), bs (broad singlet), d (doublet), triplet (t), or multiplet (m). Reference ^{1}H and ^{13}C solvent peaks included $CDCl_3$ (7.27 and 77.0), DMSO-d_6 (2.50 and 39.5), and CD_3OD (3.31 and 49.2).

Benzyl (2*S*,4*R*)-4-cyano-4-[(3-fluorophenyl)amino]-2-methylpiperidine-1-carboxylate 3b. A solution of benzyl (2*S*)-2-methyl-4-oxopiperidine-1-carboxylate[6] (31 g, 125 mmol) in acetic acid (250 mL) was treated with 3-fluoroaniline (24.1 mL, 250 mmol) followed by zinc cyanide (36.8 g, 313 mmol). The reaction mixture was stirred at room temperature for 18 h, after which it was cooled in an ice bath and slowly basified with aqueous ammonium hydroxide solution. The resulting mixture was extracted several times with dichloromethane, and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography through silica gel (20−40% ethyl acetate/heptanes) to afford a mixture of compound **3b** and its isomer benzyl (2*S*,4*S*)-4-cyano-4-[(3-fluorophenyl)amino]-2-methylpiperidine-1-carboxylate (**3a**) as an oil (36 g, 78% yield). This material was subjected to chromatography using a Chiralcel OJ-H column, 5 μm, 30 × 250 mm (Mobile phase: 70/30 CO_2/methanol; Flow rate: 120 g/min) to afford 14.6 g (32%) of **3b** as an oil: retention time 3.45−4.46 min; MS (APCI) *m*/*z* 341.1 $(M - CN)^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (m, 5H), 7.21 (m, 1H), 6.60−6.67 (m, 3H), 5.16 (dd, *J* = 12.3 Hz, 2H), 4.63 (m, 1H), 4.28 (m, 1H), 3.35 (m, 1H), 2.46 (m, 2H), 1.89 (dd, *J* = 13.9, 6.6 Hz, 1H), 1.70 (ddd, *J* = 13.3, 13.3, 4.4 Hz, 1H), 1.49 (d, *J* = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.7, 162.3, 154.8, 145.1, 136.4, 130.5, 128.6, 128.2, 127.9, 121.4, 112.7, 107.1, 104.2, 67.4, 50.0, 45.9, 39.8, 36.3, 35.8, 17.0; HRMS (ESI) *m*/*z* calculated for $C_{21}H_{22}FN_3O_2$ $[M + Na]^+$ 390.1588, found 390.1582; $[\alpha]_D^{20}$ +21.5 (*c* 1.05, CH_2Cl_2).

Benzyl (2*S*,4*R*)-4-cyano-4-[(3-ethoxy-3-oxopropanoyl)(3-fluorophenyl)amino]-2-methylpiperidine-1-carboxylate 4. 2,6-Dimethylpyridine (4.8 mL, 40.8 mmol) was added to a solution of **3b** (10 g, 27 mmol) in dichloromethane (136 mL). Ethyl 3-chloro-3-oxopropanoate (4.5 mL, 35.4 mmol) was added dropwise via an addition funnel, and the reaction mixture was stirred at room temperature for 4 h. The mixture was diluted with dichloromethane (30 mL), washed with water (80 mL), saturated aqueous sodium chloride (80 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography through silica gel (30% ethyl acetate/heptanes) to provide compound **4** (6.6 g) as a yellow oil. Mixed fractions were resubjected to flash chromatography to provide additional **4**. Total yield 8.2 g, 63%: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45−7.36 (m, 1H), 7.33−7.22 (m, 5H), 7.20−7.13 (m, 1H), 7.05−6.88 (m, 2H), 5.05 (s, 2H), 4.51 (br s, 1H), 4.20−4.11 (m, 1H), 4.06 (q, *J* = 7.2 Hz, 3H), 3.39−3.24 (m, 1H), 3.06 (d, *J* = 2.7 Hz, 2H), 2.82−2.68 (m, 1H), 2.16−2.03 (m, 1H), 1.72 (ddd, *J* = 2.0, 6.6, 13.7 Hz, 1H), 1.42 (dd, *J* = 1.4, 7.2 Hz, 3H), 1.17 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.3, 168.3, 167.3, 166.9, 166.6, 164.3, 161.8, 138.9, 136.5, 131.5, 128.7, 128.3, 128.1, 126.6, 120.3, 118.2, 118.0, 117.8, 117.6, 67.6, 61.8, 54.1, 43.5, 38.2, 32.0, 29.2, 22.8, 14.2; HRMS (ESI) *m*/*z* calculated for $C_{26}H_{28}FN_3O_5$ $[M + Na]^+$ 504.1905, found 504.1907; $[\alpha]_D^{20}$ +24.1° (*c* 1.11, CH_2Cl_2).

8-Benzyl 3-ethyl (5*R*,7*S*)-4-amino-1-(3-fluorophenyl)-7-methyl-2-oxo-1,8-diazaspiro[4.5]dec-3-ene-3,8-dicarboxylate 5. Sodium metal (426 mg, 18.5 mmol, prewashed with heptane) was added to 12 mL of ethanol and allowed to react completely. This solution of sodium ethoxide was added to a 0 °C solution of **4** (6.6 g, 14.2 mmol) dissolved in 45 mL of ethanol. The reaction mixture was warmed to room temperature, stirred for 45 min, and concentrated to provide **4** as a yellow paste (6.6 g, 100% yield), which was taken into the next transformation without purification: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.28−7.34 (m, 2H), 7.21−7.28 (m, 2H), 7.18 (d, *J* = 7.03 Hz, 2H), 7.10 (td, *J* = 2.25, 10.35 Hz, 1H), 6.99−7.06 (m, 2H), 4.83 (d, *J* = 12.50 Hz, 1H), 4.44−4.61 (m, 1H), 4.10 (q, *J* = 7.03 Hz, 2H), 3.69−3.78 (m, 1H), 3.10−3.27 (m, 3H), 2.45 (td, *J* = 1.81, 3.81 Hz, 1H), 2.30−2.42 (m, 1H), 1.92−2.04 (m, 3H), 1.16 (t, *J* = 7.22 Hz, 3H), 0.86 (d, *J* = 5.86 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 177.8, 166.9, 165.3, 163.8, 161.3, 154.1, 140.3, 137.4, 130.3, 129.0, 128.3, 128.0, 127.6, 118.5, 115.0, 88.3, 66.4, 63.0, 59.1, 55.6, 45.2, 38.5, 35.6, 33.2, 20.7, 15.1; HRMS and specific rotation data for this compound could not be obtained due to its poor solubility.

Benzyl (5*R*,7*S*)-1-(3-fluorophenyl)-7-methyl-2,4-dioxo-1,8-diazaspiro[4.5]decane-8-carboxylate 6. Compound **5** (8.0 g, 17 mmol) was added in portions to 130 mL of 6 N aqueous hydrochloric acid, and the resulting yellow suspension was heated at reflux for 28 h. After cooling to room temperature, the mixture was azeotroped several times with toluene and dried under a high vacuum for 18 h to provide a gray-green solid (assumed quantitative yield, 6.3 g). A solution of the crude intermediate (4.7 g, <15.1 mmol) in a mixture of 40 mL of tetrahydrofuran and 20 mL of water was cooled to 0 °C and treated with a solution of sodium hydroxide (4.1 g, 103 mmol) dissolved in 20 mL of water. Benzyl chloroformate (95%, 4.6 mL, 30.8 mmol) was added, and the resulting solution was stirred at 0 °C for 2 h. Another portion of benzyl chloroformate (95%, 1.28 mL, 8.6 mmol) was added, and the reaction mixture was stirred at 0 °C for an additional 2 h. The reaction mixture was concentrated under reduced pressure, and the resulting residue was diluted with 50 mL of water and extracted several times with dichloromethane. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography through silica gel (30−100% ethyl acetate/heptanes). The resulting material (5.8 g) was identified as the enol benzyl carbonate via mass spectroscopy and NMR analysis. The bulk of this material (5.0 g) was dissolved in 60 mL of tetrahydrofuran, 200 mL of 1 N aqueous sodium hydroxide was added, and the mixture was stirred for 5 h. The reaction mixture was acidified to pH 2 with 1 N aqueous hydrochloric acid and extracted several times with dichloromethane. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford compound **6** as a brown oil (1.55 g, 23%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (dt, *J* = 6.26, 8.12 Hz, 1H), 7.21−7.36 (m, 5H), 7.14 (dt, *J* = 2.15, 8.22 Hz, 1H), 6.80−6.96 (m, 2H), 4.89−5.15 (m, 2H), 4.24−4.47 (m, 1H), 4.03 (d, *J* = 12.91 Hz, 1H), 3.50 (t, *J* = 12.91 Hz, 1H), 3.50 (m, 1H), 3.36 (d, *J* = 20.0 Hz, 1H), 3.19 (d, *J* = 20.0 Hz, 1H), 1.90−2.09 (m, 2H), 1.57−1.76 (m, 2H), 1.14−1.31 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.9, 168.0, 164.1, 161.6, 136.4, 130.9, 130.8, 128.5, 128.1, 127.9, 126.3, 126.2, 118.1, 117.9, 116.7, 116.5, 111.9, 67.2, 45.8, 40.0, 35.6, 31.6; HRMS (ESI) *m*/*z* calculated for $C_{23}H_{23}FN_2O_4$ $[M + H]^+$ 411.1715, found 411.1717; $[\alpha]_D^{20}$ +32.2° c 10.0, CH_2Cl_2).

Benzyl (5*R*,7*S*)-1-(3-fluorophenyl)-4-hydroxy-7-methyl-2-oxo-1,8-diazaspiro[4.5]decane-8-carboxylate 7. A solution of compound **6** (881 mg, 2.15 mmol) in 25 mL of methanol and 5 mL of tetrahydrofuran at 0 °C was treated portionwise with sodium borohydride (248 mg, 6.42 mmol), and the resulting yellow solution was stirred at 0 °C for 2 h. The reaction mixture was quenched with 5 mL of water, the volatile components were removed under reduced pressure, and the remaining mixture was acidified to pH 3 with 1 N aqueous hydrochloric acid. The mixture was extracted several times with EtOAc (3 × 5 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography through silica gel (100% ethyl acetate) to afford compound **7** as a light brown foam (620 mg, 70%): ^{1}H NMR (400 MHz, $CDCl_3$), mixture of two diastereomers, δ 7.42−7.20 (m, 6H), 7.44−7.19 (m, 1H), 7.12−7.00 (m, 2H), 6.87−6.72 (m, 2H), 5.02 (br. s., 2H), 4.52−4.27 (m, 2H), 3.03 (t, *J* = 13.2 Hz, 1H), 2.89 (ddd, *J* = 5.4, 11.8, 17.4 Hz, 1H), 2.39 (dd, *J* = 6.3, 17.5 Hz, 1H), 2.26−1.99 (m, 1H), 1.91 (dd, *J* = 7.4, 14.3 Hz, 1H), 1.79−1.56 (m, 1H), 1.52 (d, *J* = 14.1 Hz, 1H), 1.43−1.32

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(m, 1H), 1.28−1.08 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.6, 164.2, 161.7, 136.7, 130.6, 128.2, 126.0, 118.0, 116.1, 70.1, 69.5, 68.2, 67.5, 46.5, 40.0, 36.4, 29.8; HRMS (ESI) m/z calculated for $C_{23}H_{25}FN_2O_4$ $[M + H]^+$ 413.1871, found 413.1876.

(5*R*,7*S*)-Benzyl 1-(3-fluorophenyl)-7-methyl-2-oxo-1,8-diazaspiro[4.5]dec-3-ene-8-carboxylate 8. To a solution of compound **7** (510 mg, 1.24 mmol) in 9 mL of pyridine was added thionyl chloride (0.27 mL, 3.71 mmol). The resulting mixture was stirred at room temperature for 1 h, and then at 50 °C for 18 h under a reflux condenser. The reaction mixture was cooled to room temperature, concentrated under reduced pressure, diluted with EtOAc, washed with saturated aqueous $NaHCO_3$ (4 × 10 mL), brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography through silica gel (20% EtOAc/heptanes to 100% EtOAc) to afford compound **8** as a light yellow solid (300 mg, 61%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J = 6.2 Hz, 1 H), 7.39 (dt, J = 6.3, 8.2 Hz, 1H), 7.35−7.24 (m, 5H), 7.13−7.06 (m, 1 H), 6.89−6.84 (m, 1 H), 6.81 (dt, J = 2.2, 9.3 Hz, 1H), 6.29 (d, J = 6.2 Hz, 1H), 5.05 (br. s., 2H), 4.59 (br. s., 1H), 4.20 (br. s., 1H), 3.10 (t, J = 13.4 Hz, 1H), 2.06 (dd, J = 6.6, 13.3 Hz, 1H), 1.88 (t, J = 11.6 Hz, 1H), 1.64 (br. s., 1H), 1.44 (s, 1H), 1.48 (s, 1H), 1.28 (d, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1, 164.5, 162.0, 151.2, 136.6, 131.0, 130.9, 128.7, 128.3, 128.1, 126.7, 126.6, 126.5, 118.4, 118.1, 116.2, 116.0, 100.0, 76.9, 67.6, 67.5, 46.1, 36.9; HRMS (ESI) m/z calculated for $C_{23}H_{23}FN_2O_3$ $[M + H]^+$ 395.1765, found 395.1764; $[\alpha]_D^{20}$ +18.8° (c 21.0, $CHCl_3$).

(5*R*,7*S*)-1-(3-Fluorophenyl)-7-methyl-1,8-diazaspiro[4.5]dec-3-en-2-one 9. To a solution of compound **8** (17.1 g, 43.4 mmol) in 130 mL of methanol was added 220 mL of 6 N aqueous HCl. The resulting mixture was heated at 90 °C for 6 h. The reaction mixture was cooled to room temperature, washed with EtOAc to remove any unreacted starting material, and made alkaline via the slow addition of 1 N aqueous NaOH. The aqueous phase was washed several times with EtOAc to extract the product. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography through silica gel (100% DCM to 20% MeOH/DCM) to afford compound **9** as an off-white foam (10.9 g, 97%): ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.41 (dt, J = 6.3, 8.1 Hz, 1H), 7.12 (ddt, J = 0.9, 2.5, 8.3 Hz, 1H), 7.03 (d, J = 6.0 Hz, 1H), 7.01−6.97 (m, 1H), 6.93 (td, J = 2.1, 9.4 Hz, 1H), 6.17 (d, J = 6.0 Hz, 1H), 2.90 (td, J = 4.6, 12.7 Hz, 1H), 2.74 (dqd, J = 3.3, 6.4, 9.8 Hz, 1H), 2.64 (ddd, J = 3.3, 10.9, 12.7 Hz, 1H), 2.05−1.93 (m, 1H), 1.92−1.80 (m, 2H), 1.72 (br. s., 1H), 1.65 (dd, J = 10.0, 14.2 Hz, 1H), 1.04 (d, J = 6.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 171.1, 164.2, 161.7, 155.6, 139.6, 139.5, 130.5, 130.4, 126.7, 126.6, 124.2, 118.3, 118.1, 115.9, 115.7, 67.1, 63.8, 46.9, 41.4, 33.8, 22.3; HRMS (ESI) m/z calculated for $C_{15}H_{17}FN_2O$ $[M + H]^+$ 261.1398, found 261.1399; $[\alpha]_D^{20}$ −30.8° (c 9.5, CH_2Cl_2).

(5*R*,7*S*)-1-(3-Fluorophenyl)-8-(3-isopropoxybenzyl)-7-methyl-1,8-diazaspiro[4.5]dec-3-en-2-one 1. To a stirred suspension of compound **9** (200 mg, 0.77 mmol) and potassium carbonate (322 mg, 2.30 mmol) in 4 mL of acetonitrile at 0 °C was added dropwise 1-bromomethyl-3-isopropoxy benzene (352 mg, 1.54 mmol) over several minutes. The resulting mixture was slowly warmed to room temperature and stirred for 18 h. Five milliliters of saturated aqueous NH_4Cl was added to the reaction mixture, followed by 30 mL of EtOAc. The organic layer was separated, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromtography through silica gel (25% EtOAc/heptanes) to afford compound **1** (275 mg, 87%) as a light yellow gum: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48−7.37 (m, 2H), 7.21−7.09 (m, 2H), 6.95 (d, J = 7.8 Hz, 1H), 6.89 (td, J = 2.1, 9.4 Hz, 1H), 6.83−6.72 (m, 3H), 6.23 (d, J = 5.9 Hz, 1H), 4.51 (td, J = 6.0, 12.1 Hz, 1H), 3.60 (d, J = 13.7 Hz, 1H), 3.38 (d, J = 13.7 Hz, 1H), 3.06−2.96 (m, 1H), 2.66 (ddd, J = 3.1, 9.7, 12.6 Hz, 1H), 2.46−2.37 (m, 1H), 2.13 (dd, J = 5.1, 13.3 Hz, 1H), 1.98 (ddd, J = 4.1, 9.7, 13.2 Hz, 1H), 1.72 (d, J = 12.9 Hz, 1H), 1.59 (ddd, J = 1.6, 4.7, 13.3 Hz, 1H), 1.31 (d, J = 6.2 Hz, 6H), 1.15 (d, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 164.2, 161.8, 153.7, 140.5, 137.9, 137.8, 130.5, 130.4, 129.2, 126.7, 125.0, 120.8, 118.3, 118.1, 116.2, 115.8, 115.6, 114.1, 69.7, 67.8, 58.1, 51.3, 44.3, 40.4, 33.7, 22.1, 22.0, 15.3; HRMS (ESI) m/z calculated for $C_{25}H_{29}FN_2O_2$ $[M + H]^+$ 409.2286, found 409.2287; $[\alpha]_D^{20}$ +18.1° (c 21.0, CH_2Cl_2).

(2*S*,4*S*)-Benzyl 4-hydroxy-2-methyl-4-(trichloromethyl)-piperidine-1-carboxylate 10b. A solution of **2** in DME (600 mL) was treated at room temperature with $MgCl_2$ (69.3 g, 0.73 mol) and $CHCl_3$ (58.2 mL, 0.73 mol). The reaction mixture was cooled to −78 °C and treated over a period of 1 h with a solution of LiHMDS (1.0 M in THF, 437 mL, 0.44 mol), keeping the internal temperature below −65 °C. The reaction mixture was stirred at −78 °C for two hours, after which LC−MS analysis indicated that there was less than 5% starting material remaining. The reaction mixture was warmed to −20 °C for 1 h and then cautiously quenched with H_2O (300 mL). EtOAc (300 mL) was added, and the resulting mixture was filtered through a short pad of Celite. The filter cake was washed thoroughly with EtOAc (300 mL). The layers were separated, and the aqueous layer was further diluted with water (300 mL) and re-extracted with EtOAc (600 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford a dark brown oil (88.5 g). The oil was stirred vigorously in Et_2O (120 mL) for 2 h and filtered. The collected solids were washed with Et_2O (2 × 100 mL) and dried to give alcohol **10b** as a pale brown solid, (43.6g, 49% yield): ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.36−7.23 (m, 5 H), 6.15 (s, 1 H), 5.11−4.97 (m, 2 H), 4.44 (quin, J = 7.0 Hz, 1 H), 4.00−3.89 (m, 1 H), 3.22−3.03 (m, 1 H), 2.06 (dt, J = 6.9, 13.8 Hz, 1 H), 1.95−1.75 (m, 3 H), 1.22 (dd, J = 3.7, 7.0 Hz, 3 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 154.9, 154.6, 137.6, 129.1, 128.5, 128.2, 110.8, 100.0, 80.7, 66.9, 46.2, 46.0, 35.3, 34.4, 34.1, 31.4, 31.1, 19.1, 18.4; HRMS (ESI) m/z calculated for $C_{15}H_{18}Cl_3NO_3$ $[M + Na]^+$ 388.0244, found 388.0239; $[\alpha]_D^{20}$ +34.7° (c 15.0, $CHCl_3$). An X-ray quality crystal of **10b** was grown from acetonitrile−water (obtained as white crystals, mp = 147−148 °C); see the Supporting Information for crystallographic data.

(2*S*,4*R*)-1-Benzyl 4-methyl 4-azido-2-methylpiperidine-1,4-dicarboxylate 11. A suspension of **10b** (128.4 g, 0.35 mol) in methanol (1.0 L) was treated at room temperature with 18-crown-6 ether (9.3 g, 0.04 mol) and sodium azide (68.3 g, 1.05 mol). The reaction mixture was cooled in an ice bath and treated dropwise over 20 min with DBU (262 mL, 1.75 mol). The dark brown solution was stirred at room temperature overnight (slight exotherm to 40 °C was observed upon removal of the ice bath). LC−MS analysis after 20 h showed consumption of the starting material. The reaction mixture was concentrated under reduced pressure to remove most of the methanol, and the residue was partitioned between EtOAc (1.2 L) and H_2O (1.2 L). The aqueous layer was extracted again with EtOAc (1.2 L). The combined organic extracts were washed with water, brine, dried over $MgSO_4$, and concentrated under reduced pressure to afford azide-ester **11** as a brown oil (195.2 g, 84% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40−7.28 (m, 5 H), 5.13 (s, 2 H), 4.52−4.44 (m, 1 H), 4.09−4.03 (m, 1 H), 3.83 (s, 3 H), 3.15 (ddd, J = 3.3, 12.4, 14.3 Hz, 1 H), 2.31−2.22 (m, 2 H), 1.93 (dd, J = 6.0, 13.5 Hz, 1 H), 1.60 (ddd, J = 5.2, 12.4, 13.4 Hz, 1 H), 1.08 (d, J = 7.1 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.6, 155.2, 136.8, 128.7, 128.3, 128.1, 67.5, 62.9, 53.1, 46.2, 36.8, 36.7, 32.0, 17.4; HRMS (ESI) m/z calculated for $C_{16}H_{20}N_4O_4$ $[M + Na]^+$ 355.1382, found 355.1386; $[\alpha]_D^{20}$ +4.6° (c 10.2, CH_2Cl_2).

(2*S*,4*R*)-1-Benzyl 4-methyl 4-amino-2-methylpiperidine-1,4-dicarboxylate 12. A solution of azide-ester **11** (164.4 g, 0.49 mol) in THF (1.2 L) and glacial acetic acid (1.2 L) was treated with Zn dust (<10 μm particle size, 161.3 g, 2.5 mol), and the resulting mixture was heated to 50 °C. LC−MS analysis after 4 h still showed unreacted starting material. An additional 1.0 equiv of Zn dust was added, and heating was continued at 50 °C for 10 h. The reaction mixture was cooled to room temperature. After an additional 6 h, LC−MS analysis showed the complete consumption of starting material. The reaction mixture was filtered through Celite, and the filter cake was washed thoroughly with THF (2 × 200 mL). The filtrate was concentrated under reduced pressure to remove most of the solvents, and the residue was partitioned between EtOAc (1.5 L) and saturated aqueous

$NaHCO_3$ (1.2 L). The organic layer was separated and washed again with 1.2 L saturated aqueous $NaHCO_3$. The original aqueous layer was treated with solid $NaHCO_3$ (until pH = 8−9 via litmus paper) and then further extracted with EtOAc (2 × 1 L). The combined organic extracts were washed with water, brine, dried over $MgSO_4$, and concentrated under reduced pressure to afford amino-ester **12** as a brown oil (129.2 g, 86% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.24 (m, 5 H), 5.09 (d, J = 1.4 Hz, 2 H), 4.47−4.37 (m, J = 3.6, 6.8, 6.8, 6.8, 6.8 Hz, 1 H), 4.05−3.96 (m, 1 H), 3.71 (s, 3 H), 3.12 (ddd, J = 3.0, 12.7, 14.1 Hz, 1 H), 2.21−2.09 (m, 2 H), 1.68 (dd, J = 6.1, 13.5 Hz, 1 H), 1.44−1.35 (m, 1 H), 1.01 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.5, 154.9, 137.4, 129.1, 128.5, 67.0, 55.8, 54.0, 45.5, 36.6, 36.3, 30.9, 17.3; HRMS (ESI) m/z calculated for $C_{16}H_{22}N_2O_4$ $[M + H]^+$ 307.1652, found 307.1651; $[\alpha]_D^{20}$ +20.3° (c 20.0, $CHCl_3$).

Amino ester **12** (200 mg, 0.653 mmol) was dissolved in ether (1.5 mL) and treated dropwise with 2 M HCl in ether (0.4 mL). The resulting white precipitate was filtered to afford the mono-HCl salt of **12** (202 mg). An X-ray quality crystal was grown from the salt after dissolving 53 mg of substrate in 1 mL of acetonitrile (obtained as white crystals, mp = 170−171 °C); see the Supporting Information for crystallographic data.

(2*S*,4*R*)-1-Benzyl 4-methyl 4-(3-ethoxy-3-oxopropanamido)-2-methylpiperidine-1,4-dicarboxylate 13. A solution of **12** (250.2 g, 0.82 mol) in CH_2Cl_2 (1.9 L) was cooled to 0 °C and treated sequentially with Et_3N (296.0 mL, 2.12 mol), monoethyl malonate (135.0 mL, 1.14 mol), and EDCI·HCl (219.2 g, 1.14 mol). The reaction mixture was stirred at room temperature overnight. TLC analysis (100% EtOAc) after 18 h showed complete reaction. The reaction mixture was concentrated under reduced pressure. The residue was partitioned between EtOAc (2.2 L) and 0.5 N aqueous HCl (1.5 L). The organic layer was separated, washed with 0.5 N HCl (1.5 L), saturated aqueous $NaHCO_3$ (1.5 L), brine (1.5L), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford malonamide **13** as an orange oil (322.4 g, 94% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (s, 1 H), 7.36−7.25 (m, 5 H), 5.10 (d, J = 1.4 Hz, 2 H), 4.30−4.24 (m, 1 H), 4.14 (q, J = 7.0 Hz, 2 H), 4.01−3.93 (m, 1 H), 3.70 (s, 3 H), 3.30 (ddd, J = 4.7, 11.8, 14.0 Hz, 1 H), 3.20 (s, 2 H), 2.51 (dt, J = 3.1, 14.1 Hz, 1 H), 2.12 (dd, J = 6.3, 13.8 Hz, 1 H), 2.03 (dd, J = 6.1, 13.7 Hz, 1 H), 1.64 (ddd, J = 6.2, 12.0, 14.0 Hz, 1 H), 1.24 (t, J = 7.1 Hz, 3 H), 1.12 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.5, 169.7, 164.8, 155.3, 136.9, 128.7, 128.2, 128.0, 67.3, 61.9, 56.0, 52.8, 46.0, 40.8, 37.2, 36.4, 33.3, 17.9, 14.2; HRMS (ESI) m/z calculated for $C_{21}H_{28}N_2O_7$ $[M + H]^+$ 421.1974, found 421.1969; $[\alpha]_D^{20}$ +20.3° (c 20.0, $CHCl_3$).

(5*R*,7*S*)-8-Benzyl 3-ethyl 7-methyl-2,4-dioxo-1,8-diazaspiro[4.5]decane-3,8-dicarboxylate 14. A solution of **13** (319.5 g, 0.76 mol) in EtOH (3.2 L) was treated portionwise at room temperature with sodium ethoxide (21 wt % in EtOH, 251.2 mL, 0.78 mol), and the resulting mixture was stirred at room temperature. TLC analysis (100% EtOAc) after 30 min showed complete reaction. The reaction mixture was concentrated under reduced pressure, and the resulting residue was partitioned between EtOAc (2.5 L) and 0.5 N aqueous HCl (1.5 L). The organic layer was separated, washed with water (1.5 L), brine, dried over $MgSO_4$, and concentrated under reduced pressure to afford **14** as a brown oil (284.2 g, 96% yield). NMR showed a mixture of **14** and decarboxylated material **15**. The mixture was advanced to the next step without any further purification.

(5*R*,7*S*)-Benzyl 7-methyl-2,4-dioxo-1,8-diazaspiro[4.5]-decane-8-carboxylate 15. A solution of **14** (288.3 g, 0.74 mol) in dioxane (2.2 L), acetic acid (0.85 mL, 0.015 mmol), and water (300 mL) was heated at reflux for 1 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by flash chromatography through silica gel (eluting with a sequential gradient of 100% heptanes, 50% EtOAc/heptanes, 100% EtOAc, and 10% MeOH/EtOAc) to afford **15** as a viscous amber oil (205.5 g, 88% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (br. s., 1 H), 7.35−7.24 (m, 5 H), 5.15−5.04 (m, 2 H), 4.23 (sxt, J = 6.8 Hz, 1 H), 4.04−3.95 (m, 1 H), 3.65 (s, 3 H), 3.22 (ddd, J = 4.9, 11.3, 14.3 Hz, 1 H), 3.03 (d, J = 12.0 Hz, 1H), 2.92 (d, J = 12.0 Hz, 1H), 2.09−2.01 (m, 1 H), 1.86−1.67 (m, 3 H), 1.21 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.2, 170.2, 155.3, 136.7, 128.7, 128.3, 128.0, 67.5, 67.3, 45.9, 40.1, 37.9, 36.1, 33.6, 18.9; HRMS (ESI) m/z calculated for $C_{17}H_{20}N_2O_4$ $[M + H]^+$ 317.1496, found 317.1494; $[\alpha]_D^{20}$ +60.8° (c 11.5, $CHCl_3$).

(4*R*,5*R*,7*S*)-Benzyl 4-hydroxy-7-methyl-2-oxo-1,8-diazaspiro[4.5]decane-8-carboxylate and (4*S*,5*R*,7*S*)-Benzyl 4-hydroxy-7-methyl-2-oxo-1,8-diazaspiro[4.5]decane-8-carboxylate 16. A solution of **15** (205.5 g, 0.65 mol) in methanol (2.2 L) was treated portionwise at room temperature with $NaBH_4$ (36.9 g, 0.98 mmol) over 1 h. A slight exotherm was observed, so the reaction mixture was periodically cooled with an ice bath during the addition to maintain a temperature of 25 °C. TLC analysis (10% MeOH/EtOAc) after 45 min showed a small amount of unreacted starting material. An additional 0.2 equiv of $NaBH_4$ was added. TLC analysis after 90 min showed complete reaction. The reaction mixture was slowly quenched with saturated aqueous NH_4Cl (600 mL), after which most of the methanol was removed under reduced pressure. The residue was diluted with saturated aqueous NH_4Cl (600 mL) and EtOAc (2.5 L). The organic layer was separated, washed with 0.5 N aqueous HCl (1.2 L), brine (1.2 L), dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure to afford alcohol **16** as an orange foam (176.9 g, 86% yield): ^{1}H NMR (400 MHz, $CDCl_3$) (~3:2 mixture of diastereomers) δ 7.40−7.31 (5H,m), 6.13 (0.4H, s), 6.00 (0.6H, s), 5.18−5.10 (2H, m), 4.48−4.24 (3H, m), 4.11−4.01 (1H, m), 3.19−3.04 (1H, m), 2.86−2.78 (1H, m), 2.36−2.29 (1.2H, m), 2.29−2.23 (0.8H, m), 1.82−1.56 (3H, m), 1.27 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.6, 128.5, 128.1, 127.9, 85.9, 73.0, 71.7, 67.2, 61.4, 46.2, 40.0, 36.2, 35.3, 33.7, 18.5; HRMS (ESI) m/z calculated for $C_{17}H_{22}N_2O_4$ $[M + H]^+$ 319.1657, found 319.1651.

(5*R*,7*S*)-Benzyl 7-methyl-2-oxo-1,8-diazaspiro[4.5]dec-3-ene-8-carboxylate 17. A solution of **16** (176.9 g, 0.56 mol) in CH_2Cl_2 (4 L) was treated at room temperature with methanesulfonyl chloride (51.6 mL, 0.67 mol) in one portion and then portionwise with Et_3N (108.4 mL, 0.78 mol). TLC analysis (10% MeOH/EtOAc) after 1 h showed a small amount of unreacted starting material. An additional 0.2 equiv of methanesulfonyl chloride and 0.3 equiv of Et_3N were added, and the resulting mixture was stirred for 2 h, after which TLC analysis showed complete consumption of starting material. The solution of crude mesylate was then treated portionwise with DBU (207.7 mL, 1.39 mol) at room temperature. LC−MS analysis after 1 h showed a small amount of unreacted mesylate. An additional 20 mL of DBU was added, and TLC analysis after an additional 2 h of stirring showed complete reaction. The reaction mixture was concentrated under reduced pressure to remove most of the solvents. The residue was partitioned between EtOAc (3 L) and 0.5 N aqueous HCl (1.2 L). The organic layer was separated and washed with saturated aqueous $NaHCO_3$ (1.2 L), water (1.2 L), brine (1.2 L), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford **17** a light orange foam (152.2 g, 91% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.27 (m, 5 H), 6.27 (br. s., 1 H), 6.04 (dd, J = 1.7, 6.0 Hz, 1 H), 5.12 (d, J = 3.5 Hz, 2 H), 4.58−4.48 (m, J = 3.2, 6.7, 6.7, 6.7, 6.7 Hz, 1 H), 4.19−4.11 (m, 1 H), 3.13−3.04 (m, 1 H), 1.98 (d, J = 6.4 Hz, 1 H), 2.02 (dd, J = 6.4 Hz, 12.8 Hz, 1 H), 1.88−1.79 (m, 1 H), 1.76−1.69 (dm, 1 H), 1.61 (dd, J = 1.7, 3.4 Hz, 1 H), 1.25 (d, J = 7.0 Hz, 3 H); 13C NMR (101 MHz, $CDCl_3$) δ 172.6, 155.2, 152.8, 136.8, 128.7, 128.3, 128.1, 126.5, 67.5, 62.6, 46.7, 39.6, 37.3, 34.9, 19.0; HRMS (ESI) m/z calculated for $C_{17}H_{20}N_2O_3$ $[M + H]^+$ 301.1547, found 301.1543; $[\alpha]_D^{20}$ +37.3° (c 17.5, $CHCl_3$).

(5*R*,7*S*)-Benzyl 1-(3-fluorophenyl)-7-methyl-2-oxo-1,8-diazaspiro[4.5]dec-3-ene-8-carboxylate 8. To a 250 mL reaction vessel was added compound **17** (6.0 g, 20.0 mmol), finely powdered K_3PO_4 (14.8 g, 68.3 mmol), 3-fluoro-1-iodobenzene (8.88 g, 40.0 mmol), CuI (2.2 g, 11.4 mmol), and *N*,*N*′-dimethylethylenediamine (17.3 mL, 160 mmol). The reaction vessel was tightly sealed and heated at 90 °C overnight. The reaction mixture was cooled to room temperature, diluted with EtOAc and water, and filtered through Celite. The layers were separated, and the aqueous layer was further extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude

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material was purified by flash chromatography through silica gel (0−20% EtOAc/heptanes) to afford **8** as a light yellow foam (6.62 g, 84% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J = 6.2 Hz, 1 H), 7.39 (dt, J = 6.3, 8.2 Hz, 1H), 7.35−7.24 (m, 5H), 7.13−7.06 (m, 1 H), 6.89−6.84 (m, 1 H), 6.81 (dt, J = 2.2, 9.3 Hz, 1H), 6.29 (d, J = 6.2 Hz, 1H), 5.05 (br. s., 2H), 4.59 (br. s., 1H), 4.20 (br. s., 1H), 3.10 (t, J = 13.4 Hz, 1H), 2.06 (dd, J = 6.6, 13.3 Hz, 1H), 1.88 (t, J = 11.6 Hz, 1H), 1.64 (br. s., 1H), 1.44 (s, 1H), 1.48 (s, 1H), 1.28 (d, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1, 164.5, 162.0, 151.2, 136.6, 131.0, 130.9, 128.7, 128.3, 128.1, 126.7, 126.6, 126.5, 118.4, 118.1, 116.2, 116.0, 100.0, 76.9, 67.6, 67.5, 46.1, 36.9; HRMS (ESI) m/z calculated for $C_{23}H_{23}FN_2O_3$ $[M + H]^+$ 395.1765, found 395.1764; $[\alpha]_D^{20}$ +18.8° (c 21.0, $CHCl_3$).

General Procedure for Cross-Coupling of Spirolactam 17 with Aryl Halides (Goldberg Reaction). To a 20 mL screw capped vial was added spirolactam **17** (300 mg, 1.0 mmol), finely powdered Cs_2CO_3 (985 mg, 3.0 mmol), aryl halide (2.0 mmol), CuI (96 mg, 0.5 mmol), *N*,*N*′-dimethylethylenediamine (0.75 mL, 7.0 mmol), and dioxane (5 mL). The reaction vessel was tightly sealed and heated at 90 °C for the indicated times. The reaction mixture was cooled to room temperature, diluted with EtOAc and water, and filtered through Celite. The layers were separated, and the aqueous layer was further extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography through silica gel (eluting with EtOAc/heptanes) to afford the product compound.

(5*R*,7*S*)-Benzyl 7-methyl-2-oxo-1-(pyridin-3-yl)-1,8-diazaspiro[4.5]dec-3-ene-8-carboxylate 18. Obtained 277 mg, 72% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31−8.26 (m, 1H), 7.92 (d, J = 8.2 Hz, 1H), 7.64−7.57 (m, 2H), 7.31−7.20 (m, 5H), 7.17 (s, 1H), 6.97 (ddd, J = 0.9, 4.9, 7.3 Hz, 1H), 6.16 (d, J = 6.3 Hz, 1H), 5.12−5.03 (m, 2H), 4.70−4.55 (m, 1H), 4.27−4.10 (m, 1H), 3.08 (br. s., 3H), 1.46 (br. s., 1H), 1.29 (d, J = 13.7 Hz, 1H), 1.23 (d, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.9, 152.7, 151.3, 147.5, 137.7, 136.7, 128.5, 128.0, 127.8, 125.4, 120.2, 118.6, 69.1, 67.2, 46.1, 37.0; HRMS (ESI) m/z calculated for $C_{22}H_{23}N_3O_3$ $[M + H]^+$ 378.1812, found 378.1817; $[\alpha]_D^{20}$ +15.7° (c 10.1, $CHCl_3$).

(5*R*,7*S*)-Benzyl 7-methyl-2-oxo-1-(pyrazin-2-yl)-1,8-diazaspiro[4.5]dec-3-ene-8-carboxylate 19. Obtained 259 mg, 69% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33−8.18 (m, 1H), 7.92 (d, J = 8.2 Hz, 1H), 7.70−7.44 (m, 2H), 7.37−7.20 (m, 5H), 7.17 (s, 1H), 6.97 (ddd, J = 0.9, 4.9, 7.3 Hz, 1H), 6.16 (d, J = 6.3 Hz, 1H), 5.15−4.97 (m, 2H), 3.08 (br. s., 3H), 1.46 (br. s., 1H), 1.29 (d, J = 13.7 Hz, 1H), 1.23 (d, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.64, 153.75, 148.29, 141.01, 140.04, 139.59, 136.58, 128.51, 128.09, 127.88, 124.98, 77.32, 77.00, 76.68, 69.16, 67.32, 46.02, 36.84; HRMS (ESI) m/z calculated for $C_{21}H_{22}N_4O_3$ $[M + H]^+$ 379.1765, found 379.1766; $[\alpha]_D^{20}$ +7.9° (c 10.7, CH_2Cl_2).

(5*R*,7*S*)-Benzyl 7-methyl-1-(1-methyl-1*H*-pyrazol-4-yl)-2-oxo-1,8-diazaspiro[4.5]dec-3-ene-8-carboxylate 20. Obtained 240 mg, 63% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, J = 6.2 Hz, 1 H), 7.41 (s, 1 H), 7.39−7.26 (m, 5 H), 6.27 (d, J = 6.2 Hz, 1 H), 5.09 (br. s., 2 H), 4.65 (br. s., 1 H), 4.21 (br. s., 1 H), 3.89 (s, 3 H), 3.11 (br. s., 1 H), 2.17 (dd, J = 6.7, 13.6 Hz, 1 H), 1.94 (br. s., 1 H), 1.55 (br. s., 1 H), 1.38 (d, J = 13.3 Hz, 1 H), 1.29 (d, J = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 151.2, 137.3, 136.4, 128.5, 128.3, 128.1, 127.9, 126.1, 67.4, 66.3, 39.5, 36.5; HRMS (ESI) m/z calculated for $C_{20}H_{21}N_3O_3S$ $[M + H]^+$ 384.1376, found 384.1380; $[\alpha]_D^{20}$ +13.1° (c 20.4, CH_2Cl_2).

(5*R*,7*S*)-Benzyl 7-methyl-2-oxo-1-(thiazol-4-yl)-1,8-diazaspiro[4.5]dec-3-ene-8-carboxylate 21. Obtained 270 mg, 71% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (d, J = 2.3 Hz, 1 H), 7.88 (d, J = 2.3 Hz, 1 H), 7.66 (d, J = 6.2 Hz, 1 H), 7.42−7.29 (m, 5 H), 6.27 (d, J = 6.2 Hz, 1 H), 5.26−5.12 (m, 2 H), 4.72 (br. s., 1 H), 4.28 (br. s., 1 H), 3.17 (br. s., 2 H), 3.12−3.01 (m, 1 H), 1.55 (d, J = 12.1 Hz, 1 H), 1.44−1.27 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 151.9, 149.7, 147.4, 136.6, 128.5, 128.0, 127.8, 125.1, 106.2, 99.7, 68.7, 67.2, 46.0, 36.9; HRMS (ESI) m/z calculated for $C_{21}H_{24}N_4O_3$ $[M + H]^+$ 381.1921, found 381.1925; $[\alpha]_D^{20}$ +16.9° (c 10.3, CH_2Cl_2).

(5*R*,7*S*)-Benzyl 1-(5-chloropyridin-3-yl)-7-methyl-2-oxo-1,8-diazaspiro[4.5]dec-3-ene-8-carboxylate 22. Obtained 288 mg, 70% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (s, 1H), 8.29 (s, 1H), 7.69 (d, J = 6.2 Hz, 1H), 7.52 (s, 1H), 7.40−7.30 (m, 5H), 6.35 (d, J = 6.0 Hz, 1H), 5.10 (br. s., 2H), 4.67 (br. s., 2H), 4.28 (br. s., 2H), 3.16 (t, J = 12.4 Hz, 2H), 2.03 (dd, J = 6.5, 13.4 Hz, 2H), 1.94−1.66 (m, 4H), 1.55 (d, J = 12.7 Hz, 2H), 1.33 (d, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.8, 151.5, 148.8, 148.4, 138.0, 136.1, 128.4, 128.0, 127.8, 125.8, 81.9, 67.3, 45.7, 38.0, 36.4, 33.5; HRMS (ESI) m/z calculated for $C_{22}H_{22}ClN_3O_3$ $[M + H]^+$ 412.1422, found 412.1420; $[\alpha]_D^{20}$ +22.5° (c 10.0, CH_2Cl_2).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra, and single crystal X-ray crystallographic data (CIF) for compounds **10b** and **12**. 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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