PRACTICAL MULTIGRAM APPROACH TO CONFORMATIONALLY CONSTRAINED PROLINE-BASED BUILDING BLOCKS WITH γ-SPIRO CONJUNCTION

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ABSTRACT

Unusual amino acids have arisen as an indispensable instrument at the disposal of modern medicinal chemistry. While extensively exploited as building blocks in the search for new pharmaceuticals, their application goes far beyond and they are currently involved in the exploration of the structure and conformational mobility of peptides, modification and amplification of peptidomimetics' activity, and others. Herein, we communicate an effective synthetic approach to non-planar, conformationally restricted, sp^3-enriched spirocyclic α-prolines. The protocol employs readily available nitrile starting materials and conventional experimental procedures. The synthetic sequence is concise and includes three principal stages (one of them is a 4-step through process). The reactions proceed on a multigram scale affording the target prolines in overall good yields. The building blocks synthesized in the study are expected to have practical uses in the field of medicinal chemistry.

INTRODUCTION

Over the last two decades, medicinal chemistry has witnessed a gradual change in priorities that concerns the repertoire of building blocks for the design and synthesis of pharmaceutical agents. In this way, the notions of "scaffold hopping",[1] "escape the flatland"[2] and "conformational restriction"[3,4] have become the primary distinguishing features in the realm of bioactive compounds. While chasing novel chemical entities during lead optimization programs in order to replace an 'old' plane core structure and thus reach a drug candidate, chemists increasingly turn their sight to 3D-shaped constructions.[5,6] This trick often enables researchers to keep the desirable activity of the molecule and simultaneously improve different aspects of its ADMET profile as well as maximize the success rate of MedChem projects. Among known sophisticated three-dimensional templates, a particularly intriguing case is spirocyclic compounds, which are conformationally constrained carcasses allowing for well-defined vectorization in all three dimensions.[7] This unique quality of spirocyclic motifs secures specific orientation of the functional fragments within the molecules, thus making possible purposeful elongation of the molecular framework

into distinct directions. The exploration of spirocyclic compounds has paved the way for practical applications of those scaffolds and they have contributed to a variety of approved drugs and drug candidates so far.[8,9] However, along with the undeniable attractiveness of spirocycles for MedChem investigations, their density and rigidity pose significant challenges in their construction. Due to the symbiotic evolution of drug discovery and synthetic organic chemistry and their strong mutual impact,[10] a wide range of reaction pathways for creating specific spirocyclic structures have been elaborated, thus enhancing the variety of spirocyclic systems. Nevertheless, as evidenced by our years' experience in producing MedChem-relevant building blocks with spiro conjunction,[11-14] the chemical space of spirocycles is still in its infancy. This fact significantly interferes with further rational utilization of these motifs and slows down the drug discovery process.

As part of our ongoing efforts on the design and synthesis of advanced building blocks for medicinal chemistry, quite recently we have reported two practical multigram protocols to reach spirocyclic proline topology with a spiro portion in position 3 of the pyrrolidine ring.[15] This work was motivated by several reasons. First, natural products serve as privileged templates in the discovery of modern drugs, thus giving inspiration for many researchers.[16,17] Secondly, while natural amino acids do hold the role of much-renowned bioactive compounds from the earliest days of medicinal chemistry,[18] their 'unusual' counterparts have broken into MedChem protocols lately and have already risen to indispensable components of modern medicinal chemistry. A comprehensive review on the issue[19] outlined three essential components of their success, including the desire to reach non-flat templates, increasing recognition of peptides and modified peptides as pharmaceutical agents,[20] and ever-growing commercial availability of amino acids with diverse side chains[21]. The construction of peptidomimetics is particularly a fascinating way of utilizing 'unusual' amino acids.[22] The altered structure of these small protein-like chains is designed to mimic native counterparts and advantageously adjust pharmacological properties such as stability or biological activity. This direction in MedChem research has already unleashed its power and relevance, especially in the creation of anticancer and antiviral agents and now many peptidomimetics are marketed FDA-approved drugs.[23,24] Among others, prominent examples include romidepsin and bortezomib (both anti-cancer), atazanavir and saquinavir (both *anti*-HIV), nirmatrelvir (*anti*-COVID-19), oktreotid (somatostatin mimic). Thereby, fully realizing that the success of MedChem projects directly depends on the diversity of available chemical libraries and how easily they can be achieved,[25] herein we describe a practical multigram approach to conformationally constrained proline-based building blocks with γ-spiro conjunction. This work is a direct continuation of our previous research and is intended to support the drug design of novel peptidomimetics and related pharmaceutical agents.

Remarkably, former investigations have already revealed the utility of γ-spiro proline fragment for the creation of potent bioactive substances, mostly with *anti*-HCV activity[26-28] (Figure 1, A). Thus, the synthetic route to ledipasvir (FDA-approved in 2014) employs proline with spirocyclopropane fragment. Another interesting case is a new HCV NS3/4A inhibitor (MK-8831), which was obtained by introducing a γ-spirocyclic proline surrogate onto a macrocyclic core of grazoprevir, hence injecting greater conformational rigidity to the molecule and biasing it toward the bioactive conformation.[29,30] Also, a new proline-based chemotype was discovered as TPH1 inhibitors, providing an attractive starting point for subsequent optimization of the inhibitors' efficacy.[31,32] Spirothioketal peptide-like ACE inhibitor spirapril belongs to the group as well.[33]

Interesting non-planar molecular template and tangible MedChem impact of the spiro proline building blocks tempted researchers into elaborating several synthetic strategies toward them. An overview of existing approaches is given in Figure 1(B). One of the first methods was reductive cyclization of carbon-centered glycine radicals (**I**), which does have theoretical value but is impractical due to low yields and selectivity.[34] Since then, several alternative synthetic schemes have been designed. In quest for potent and selective cathepsin C inhibitors, *Banerjee et al.* prepared several prolines with a carbocyclic 4-spiro moiety of various sizes (**II**). The synthesis commenced from hydroxymethyloxirane and after 5 stages provided the target prolines in a low 6-12% overall yield.[35] A series of 1,3-dipolar cycloaddition protocols are known to reach the discussed framework. The reported procedures generally involve the construction of spiroisoxazoline derivatives based on *exo*-CH_2-prolines reacting with *in situ* generated nitrile oxides (**III**).[36,37] Interestingly, one of the documented isoxazolines is a clinical candidate against HCV virus.[28] A related cascade approach was communicated by *Gao et al.* that employs $Cu(NO_3)_2$ mediated regioselective [2+2+1] cyclization of terminal alkynes with 4-methyleneproline (**IV**).[38] Although furnishing the target spirocyclic carcass in one step with good yields and diastereoselectivity, the method is inherently limited by the products' diversity. Alternative catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylides with a range of 2-alkylidenecycloketones afforded polysubstituted prolines with spiro quaternary stereogenic carbon center in sub-mmol scale and promoted by AgOAc/TF-BiphamPhos catalytic system (**V**).[39] The ring-closing metathesis reaction was shown to be a possible way to assemble 4-spiro prolines with a cyclopentane portion, though it suffered from small scales (**VI**).[40,41] Other reported methods were specifically designed for the preparation of certain conformationally restricted prolines and include visible light-mediated transformations of activated carboxylic acids catalyzed by $Ir(ppy)_2(dtbbpy)PF_6$, and applied to the synthesis of spirobutenolides,[42] Michael addition of a methyl 1,4-dihydrobenzoate derived anion to a dehydroalanine derivative,[43] the intramolecular aminohydroxylation of N-homoallylsulfonamides followed by oxidation.[44,45] While most of the mentioned methods have obvious

shortcomings for the multigram preparation of a wide range of spiro prolines, a noteworthy focus is on a synthetic pathway developed by chemists from GlaxoSmithKline (**VII**). This pathway was created as a means of investigating various spiro proline patterns in new HCV NS5A inhibitors.[27] The general approach to compounds in the 4-spiro proline series starts from cyclic esters and goes through successive formation of corresponding aldehydes, imines, and oxazines. The latter, subjected to the Ranay Ni-mediated ring contraction, afforded the target spirocyclic esters. Seemingly efficient and versatile, the protocol might have solved the problem of preparing diverse 4-spiro proline building blocks on a large scale. However, the authors did not share both experimental procedures for the intermediates and final products, and their spectral characteristics as well. In light of this, it is difficult to judge how practical the proposed avenue is.

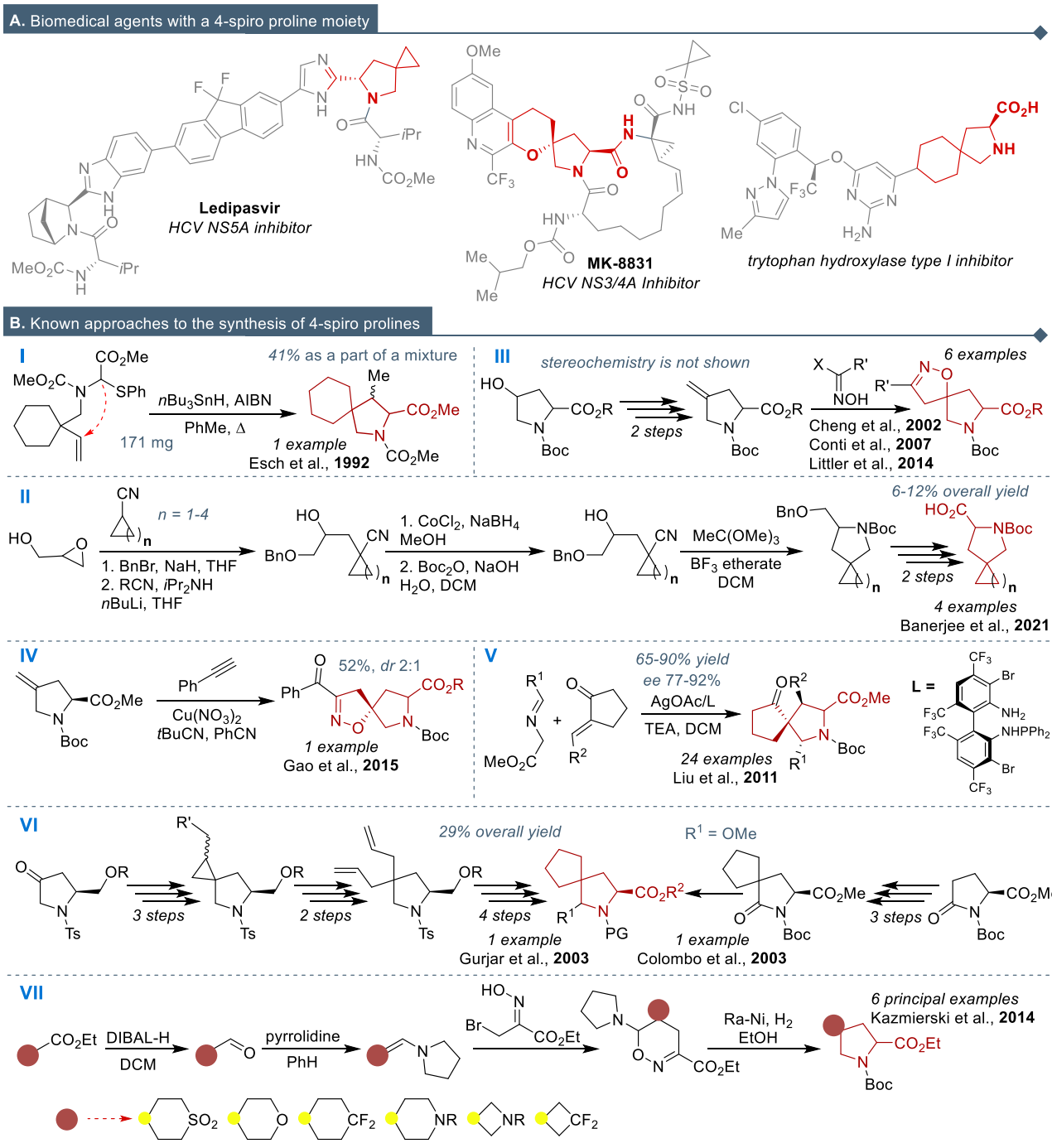

Figure 1. Known bioactive 4-spiro prolines (A) and reported methods for their synthesis (B)

Therefore, considering existing inconveniences we decided to find the most appropriate strategy for the preparation of 4-spiro prolines, which are required for our in-house MedChem program on search of peptidomimetics acting as enzyme inhibitors. This devised strategy should apply to a wide range of starting compounds, operate common chemicals and typical procedures from laboratory practice, and be easily scalable. We did find a method meeting all the requirements. In fact, this work by *Teetz and Gaul*[46] was historically the first method to achieve the discussed topology. It utilizes cyclohexanecarbonitrile and after 6 stages leads to the desired spiro proline template. Despite evident advantages, the described pathway also has weak sides that prevent its application as is. Firstly, procedures are not detailed, and some steps are even missed in the experimental section. Secondly, the route was tested only on one derivative, and it is not clear if the method is relevant for other nitriles. Therefore, to clarify all the issues and evaluate the boundaries of the method, thus providing a viable avenue toward value-added 4-spiro proline chemicals, herein we report the results of our investigation of the route.

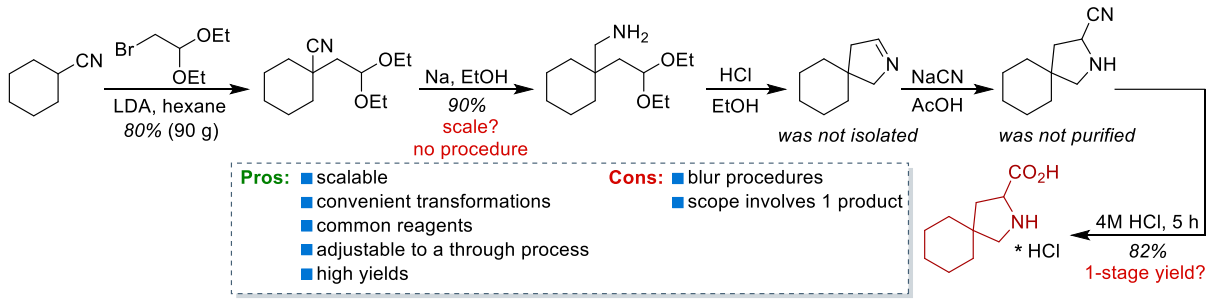

Figure 2. Outline of the *Teetz and Gaul* work

RESULTS AND DISCUSSION

The initial optimization of the literature synthetic sequence started with minor modifications of *Step 1* (Figure 3, A). To this end, we used cyclohexanecarbonitrile (**1d**) as the initial compound to compare our findings with the reported protocol. First, we employed the starting nitrile as a solution in THF. This modification would allow for further use of solid nitriles and make experimental procedure handier. In this regard, a co-solvent for the LDA solution was also changed to THF. Additionally, the order of mixing the reagents at this stage was altered so that the generation of carbanion was carried out by adding the base solution to the nitrile/THF mixture. These modifications slightly improved the yield of acetal **2d** to 85% and the procedure worked well with an even larger scale of the nitrile furnishing 134 g of the product **2d**. Noteworthy, we established that the full conversion of the starting compounds can be achieved within 12 hours at room temperature without a need to keep the low temperature for 24 hours as the original protocol claims. Next, we proceeded to *Step 2*. Since only a simple description of the step was provided in the *Teetz's* work, we decided to use more reliable LAH/THF conditions for the reduction of the nitrile

function, instead of the reported Na/EtOH system. As we found out, the reaction occurred smoothly in a good 83% yield and 115 g scale of amine **3d**. The following *Steps 3-6* were realized in a telescopic manner as in the original method. The only difference concerned the purification of the crude hydrochloride **6**. While in the *Teetz's* paper it was recrystallized from appropriate solvents (that raises some doubts), we obtained pure spirocyclic amino acid in *N*-Boc protected form. This decision simultaneously enabled us to isolate pure spiro proline **7d** and reach a convenient protected form for the use in subsequent transformations, e.g. peptide couplings. The total 4-step yield of proline **7d** was 62% (99 g), which corresponds to a formal 89% on each step. Hence, the collected results evidence the feasibility of the modified procedure for further evaluation against other substrates.

The following investigations were performed with a series of starting carbocyclic nitriles with 3 to 5 ring size. Beyond that, we tested functionalized 6-membered nitriles, including those with 4,4-*di*-F-cyclohexyl, 4-(thio)pyranyl and 4-piperidyl cores. Another 'peculiar' object of the study was isobutyronitrile. Despite acyclic nitriles seeming to be out of the scope of the current work, we included the latter into a shortlist as such a side chain in the starting compound still creates quaternary carbon in position 4 of the pyrrolidine moiety and gives rise to a distinct 3D shaped topology that resembles spirocyclic counterparts.

Having outlined the working space, we exposed all the nitriles to the elaborated protocol. The first limitation that emerged during the experiments was cyclopropanecarbonitrile. For the 3-membered ring, we did not even manage to obtain 1st step product – acetal **2**, instead the isolated material constituted a complex mixture (according to ^{1}H NMR and HPLC) and its separation served no purpose. This result was obtained for all the tested conditions (including the standard ones), e.g. LDA/THF/-78°C→rt, LDA/DMEDA/THF/-78°C→rt, NaHMDS/THF/-78°C→rt. Apparently, the applied bases provoked a ring-opening destruction of the cyclopropyl portion. Similar behavior was also observed for *N*-protected piperidine derivatives (*N*-Boc, *N*-Cbz and *N*-Bn). The latter did not furnish the target acetals **2** despite variation of bases (LDA, NaHMDS, LiHMDS), temperature modes (-78 to 60°C), and adding complexing agents. Generally, other examined starting compounds did not lead to unexpected results and reacted conventionally throughout the synthetic sequence with comparable yields for structurally related compounds. As a result, the target *N*-Boc amino acids **7a-g** were obtained in 22-44% overall yield and up to 137 g scale (Figure 3, B).

In spite of the reactions proceeded smoothly, some practically valuable aspects should be discussed in detail. Thus, while isolating compounds **2a-c** with low boiling points vacuum evaporation should be conducted at the bath temperature of 25-30°C to avoid the loss of the products. The same precaution should be taken in *Step 2*, as amines **3a-c** are also substances with low boiling points and, what is more, capable of forming azeotropes with the solvent THF. In this way, on increasing dilution, the yields

are usually lowered. It was also determined experimentally that the use of freshly prepared LDA solution is a crucial factor to reach the reported yields of nitriles **2**, especially for the low-molecular-weight members. The most challenging was intramolecular cyclization to form imines **4** (*Step 3*). In fact, this step is a 2-stage process involving consecutive acid-catalyzed hydrolysis of acetal and subsequent cyclization of the ammonium salt under the treatment with NaOH. The first stage is quite sensitive to the pH value of the solution and the amount of the acid added. Thus, the reaction was very slow when an HCl solution with less than 2 M concentration was utilized (0.5 mL of the acid solution per 1 mmol of a substance). At the same time, the use of higher than 1 M concentrations of the substance caused tarring, presumably because of intermolecular cross-linking processes. Also, according to the original procedure, the acidic solution should then be quickly adjusted to pH 5 with 2 M NaOH. However, such an order of mixing the reagents led to low yields of the crude imines. Again, the reason behind that might be unwanted intermolecular interactions. A possible answer to the problem being the addition of the NaOH solution in one portion is not applicable due to a highly exothermic reaction, especially in the case of multigram loads. To overcome the problem we applied a reverse order of mixing the reagents, thus adding an acidic solution of the aminoaldehyde to a 3 M NaOH solution. Imines **4** were promoted to the next step without purification, though they can be isolated in a pure state by careful vacuum distillation. In the case of using crude imine, the only option to introduce the nitrile function is the utilization of a cyanide salt (either Na or K). Otherwise, pure imine can cleanly react with TMSCN to give the intermediate nitrile **5** in comparable efficacy. For the conversion of the nitriles into carboxylic acids, we tested both acidic and basic hydrolysis. It was found out that either of the alternatives is suitable for the purpose, though acid-catalyzed transformation usually allows for better yields of compounds **6**. Nonetheless, for acid-intolerant substrates, a base-mediated hydrolysis could be a perfect choice.

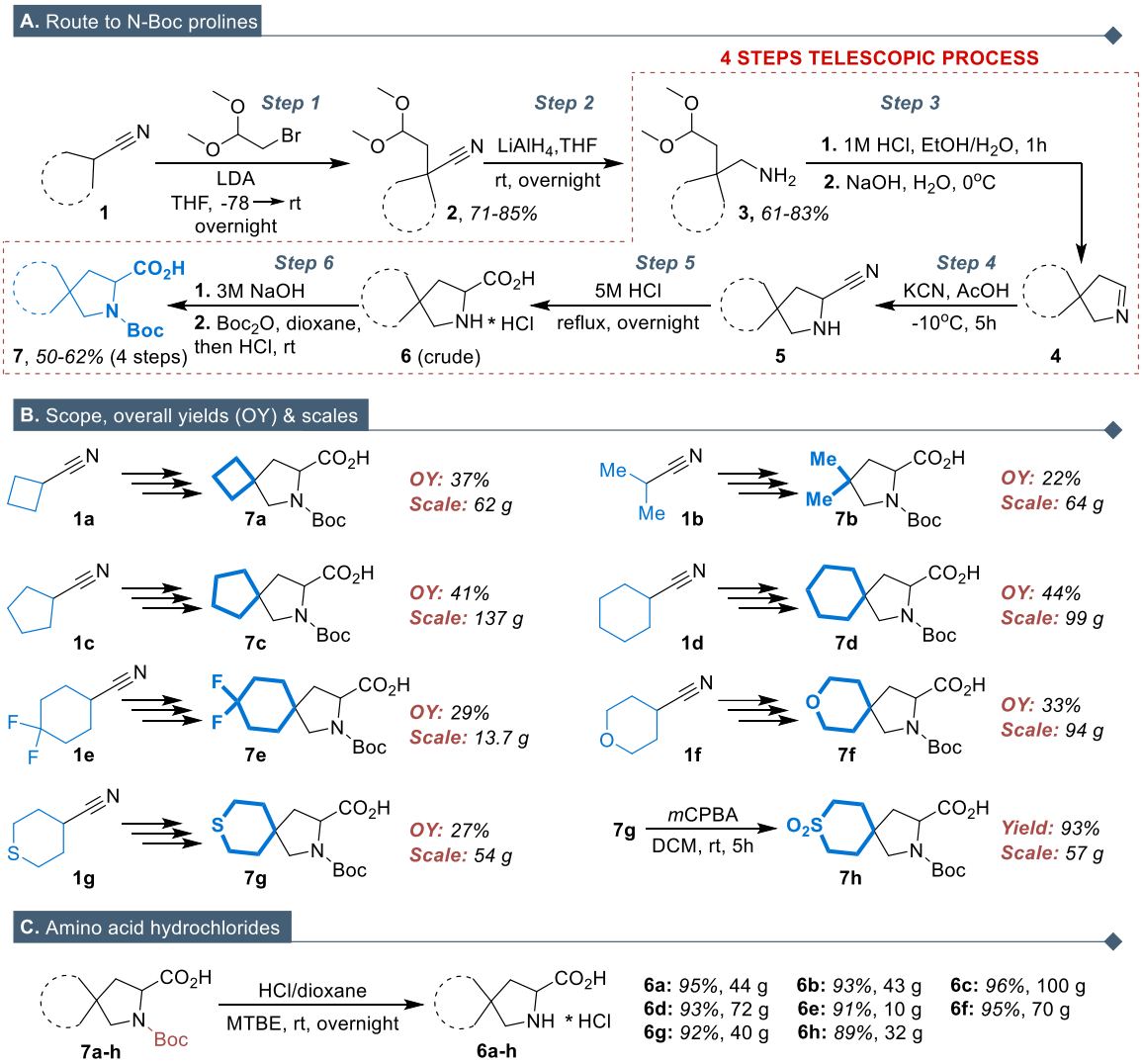

Figure 3. Synthetic pathway to the target 4-spiro prolines (A), scope and yields of the obtained compounds (B), and synthesis of *N*-unprotected amino acid hydrochlorides (C)

Interestingly, in the work by *Kazmierski et al.,* the preparation of *N*-Cbz analog of compound **7e** was accomplished in a quite complicated way. Thus, the *gem-di*-F portion was introduced into the already assembled spiro proline core using deoxofluorination with Deoxo-Fluor and in pure yield of 23%. Moreover, the reaction produced an inseparable mixture of the target *gem-di*-F derivative and the corresponding dehydrofluorination product. This complication demanded additional synthetic operation that indeed lowered the total yield. The proposed in this work procedure is an excellent alternative to obtain such a scaffold with a reputable sp^3-enriched fluorinated fragment.

Besides, it is worth noting that compound **7g** was hitherto unknown. Considering the recent progress in the field related to the studies of biochemical pathways of thiopyrans[47] and the recent idea claiming the substitution of oxygen by sulfur in a tetrahydropyrane core may have a beneficial effect on the bioactivity[48] make this spiro proline invaluable investigational material for the researchers. Moreover, closely related thiopyran S,S-dioxides are also experiencing intense studies nowadays having led to marketed antiviral amenamevir[49] and potent agents for the

treatment of inflammation-associated disorders[50]. We thereby performed oxidation of **7g** to corresponding sulfone **7h** with H_2O_2 with excellent yield and multigram scale.

Finally, we obtained amino acid hydrochlorides **6a-h** as they are widely utilized building blocks in MedChem research. Compounds **6** were synthesized by conventional Boc-deprotection of acids **7** with HCl/dioxane solution in 89-96% yield and up to 100 g scale.

CONCLUSIONS

In summary, unusual α-amino acids have gained significant importance and become a desirable molecular platform due to their inherent biological activity and ability to modify the structure of physiologically active peptides. In this regard, proline analogs constitute a unique group of unusual α-amino acids characterized by distinctive structural restrictions and, thus, occupy a prominent place in studying the receptor affinity and biological activity of peptidomimetics. Therefore, the pathways to and uses of proline-based topologies are in the constant spotlight of specialists from both synthetic organic chemistry and biochemistry.

In this work, we have reported the facile and concise preparation of a series of *N*-Boc-protected 4-spiro prolines from readily available cyclic carbonitriles. The synthetic strategy includes six simple and handy transformations and utilizes ordinary inexpensive chemicals. Four out of six steps can be realized as a through process that substantially increases the practicability of the elaborated protocol. The target *N*-Boc amino acids were obtained in good overall yields and multigram scales, thus opening access to a collection of building blocks for the construction of compounds with potential pharmaceutical applicability. The found and discussed features of the synthetic steps will surely reinforce researchers with a convenient instrument for the further expansion of chemical space of such value-added prolines with a high level of three-dimensionality.

EXPERIMENTAL PART

All starting compounds were obtained from commercial sources and used without additional purification. All solvents were purified according to the standard procedures.

1.37 M solution of LDA was prepared from interaction of *n*BuLi (1 equiv, 2.5 M solution in hexanes) with diisopropylamine (1.05 equiv) in THF (0.32 mL per 1 mmol of diisopropylamine) under Ar atmosphere and used immediately after preparation.

^{1}H NMR spectra were recorded on a Varian Unity Plus 400 (400 MHz) or a Bruker 170 Avance 500 (500 MHz) instrument; ^{13}C NMR spectra were recorded on a Bruker 170 Avance 500 (126 MHz) or an Agilent ProPulse 600 (151 MHz) spectrometer; ^{19}F NMR spectra were recorded on a Varian Unity Plus 400 (376 MHz) instrument. The NMR chemical shifts are referenced using the solvent signals at 7.26 and 77.1 ppm for ^{1}H and ^{13}C nuclei, respectively, in $CDCl_3$, and 2.48 and 39.5 ppm for ^{1}H and ^{13}C nuclei,

respectively, in DMSO-d_6; C_6F_6 was used as the internal standard for ^{19}F NMR spectra. LCMS and GCMS analyses were performed with assistance of an Agilent LC/MSD SL 1100 instrument (atmospheric pressure electrospray ionization (ES-API)) or an Agilent 5890 Series II 5972 GCMS instrument (electron impact (EI) ionization (70eV)), respectively. Results for elemental analysis were obtained at the Analytical Laboratory of the Institute of Organic Chemistry of the National Academy of Sciences of Ukraine. A composition of the hydrochloride salts was established by an acid-base titration method. Melting points were determined on an MPA100 OptiMelt automated melting point system.

According to ^1H and ^{13}C NMR spectra, *N*-Boc amino acids **7** exist as two major rotameric forms in the solution.

GENERAL PROCEDURE FOR THE SYNTHESIS OF *N*-BOC PROLINES 7

STEP 1. Alkylation with 2-bromoacetaldehyde dimethyl acetal

Nitrile **1** was dissolved in dry THF (1 mL per 1 mmol of a nitrile), and the solution was cooled to –78°C. Then 1.37 M solution of LDA (1.2 equiv) was added dropwise to the mixture. After stirring for 1 hour, 2-bromoacetaldehyde dimethyl acetal (1.05 equiv) was added dropwise. Upon completion of the addition, the reaction mixture was allowed to slowly warm to room temperature and then stirred overnight. The solvent was evaporated under reduced pressure, and the resulting residue was partitioned between MTBE (1 mL per 1 mmol of the nitrile) and water (1 mL per 1 mmol of the nitrile). The organic layer was separated, dried over Na_2SO_4, concentrated under reduced pressure, and the obtained residue was distilled to obtain pure compound **2**.

STEP 2. Reduction of nitriles 2

$LiAlH_4$ (2 equiv) was carefully added to dry THF (2 mL per 1 mmol of $LiAlH_4$). To the resulting mixture, a THF solution of nitrile **2** (1 equiv, 0.25 mL THF per 2 mmol of the nitrile) was added dropwise at such a rate to prevent boiling. After stirring overnight at room temperature, water (1.2 equiv) was added dropwise to the reaction mixture, followed by a 1 M solution of NaOH (1.2 equiv), and then water again (3.6 equiv). The mixture was filtered, and the obtained solution was concentrated under reduced pressure. Primary amine **3** thus obtained was used in the next step without additional purification.

STEPS 3-6. Telescopic process to the target *N*-Boc amino acids

Amine **3** was added to a mixture of ethanol and 2 M HCl (0.5 mL of both solvent and reagent per 1 mmol of substance) and the resulting mixture was stirred for 1 hour. Upon completion, the mixture was added (quickly and dropwise to prevent the temperature of the resulting reaction mixture from rising higher than rt) to a cooled 3 M NaOH water solution (1.2 mmol of NaOH per 1 mmol of the substance). Then, the mixture was rapidly cooled to –10°C followed by adding ice-cold acetic acid (0.25 mL per 1 mmol of **3**) and potassium cyanide (2.0 equiv). The mixture was stirred for 5 hours, then conc. HCl (0.5 mL per 1 mmol of **3**) was added, and the mixture was

refluxed overnight. After that, the solution was evaporated to dryness affording crude amino acid hydrochlorides **6**, which were directly employed further without purification.

A solid of crude hydrochloride **6** was dissolved in a solution of 3 M NaOH (0.5 mL per 1 mmol of compound **6**, the content by ^{1}H NMR), and a solution of Boc_2O (1.2 equiv) in dioxane (1 mL per 1 mmol of Boc_2O) was added dropwise at room temperature. The reaction mixture was let to react overnight while stirring, and the obtained solution was concentrated under reduced pressure. The resulting residue was partitioned between MTBE (1 mL per 1 mmol of **6**) and water (1 mL per 1 mmol of **6**). The obtained alkaline water solution was acidified with 2 M HCl to a slightly acidic pH. The solution was then extracted with EtOAc (3 times, 0.5 mL per 1 mmol of **6**). The resulting solution was then concentrated *in vacuo* giving pure *N*-Boc proline **7**.

Procedure for the oxidation of thiopyran 7g

To a mixture of 100 mL of water, 9.5 mL of 50% aqueous sodium hydroxide, and 2.5 g (0.01 mol) of tungstic acid *N*-Boc amino acid **7g** (60.2 g, 0.2 mol) was added. The resulting solution was heated to 45°C and 35% hydrogen peroxide (104 mL, 1.0 mol) was slowly added (control of the temperature within 40-45°C, not lower than 40°C). Then the reaction mixture was allowed to stir at 47-48°C for 5 hours, followed by cooling to rt, filtering over a thin pad of celite, and rinsing with water (2×30 mL). After that 5 M HCl was carefully added to pH 4-5, the solution was cooled to 0°C and stirred for 1 hour. The obtained solid was filtered off, washed with cold water (2×30 mL), and dried under reduced pressure providing the target sulfone **7h**.

Procedure for the deprotection of *N*-Boc prolines 7

A protected amino acid **7** was dissolved in MTBE (1 mL per 1 mmol of **7**) at room temperature. While stirring a solution of HCl in dioxane (0.5 mL per 1 mmol of **7**) was added dropwise, and the mixture was stirred overnight. A precipitate formed was filtered, washed with MTBE, and dried under reduced pressure.

1-(2,2-Dimethoxyethyl)cyclobutane-1-carbonitrile (2a)

Yield: 91 g, 82% (from 53 g of **1a**). Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.54 (td, J = 5.8, 1.8 Hz, 1H), 3.38 (s, 6H), 2.53 – 2.46 (m, 2H), 2.23 – 2.15 (m, 3H), 2.04 – 1.97 (m, 3H). ^{13}C NMR (126 MHz, DMSO-d_6): δ = 124.42, 102.15, 53.09, 40.39, 32.53, 31.99, 16.71. GCMS: 138.0 $[M\text{-}OCH_3]^+$. Anal. Calcd for $C_9H_{15}NO_2$: C, 63.88; H, 8.93; N, 8.28. Found: C, 63.72; H, 9.01; N, 8.34.

(1-(2,2-Dimethoxyethyl)cyclobutyl)methanamine (3a)

Yield from **2a**: 74 g, 79%. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.27 (t, J = 5.0 Hz, 1H), 3.28 (s, 6H), 2.65 (s, 2H), 1.91 – 1.61 (m, 10H). ^{13}C NMR (126 MHz, DMSO-d_6): δ = 102.43, 52.26, 48.59, 41.01, 39.10, 29.10, 14.89. LCMS: $[M + H]^+$ 174.2. Anal. Calcd for $C_9H_{19}NO_2$: C, 62.39; H, 11.05; N, 8.08. Found: C, 62.48; H, 10.98; N, 8.15.

6-Azaspiro[3.4]octane-7-carboxylic acid hydrochloride (6a)

Yield from **7a**: 44 g, 0.23 mol, 95%. Brown powder. Mp 137−141 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.59 (s, 1H), 8.75 (s, 1H), 4.21 (s, 1H), 2.35 (dd, J = 13.0, 8.3

Hz, 1H), 2.13 – 1.72 (m, 8H). ^{13}C NMR (151 MHz, DMSO-d_6): δ = 170.82, 58.14, 55.29, 44.64, 40.61, 31.66, 30.82, 15.91. LCMS: [M - Cl]$^+$ 156.2. Anal. Calcd for $C_8H_{14}ClNO_2$: C, 50.14; H, 7.36; N, 7.31. Found: C, 50.05; H, 7.43; N, 7.19.

6-(*tert*-Butoxycarbonyl)-6-azaspiro[3.4]octane-7-carboxylic acid (7a)

4 Steps yield from **3a**: 62 g, 0.24 mol, 57%. Light-brown powder. Mp 116−119 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.62 (s, 1H), 4.37 – 4.16 (m, 1H), 3.59 – 3.34 (m, 2H), 2.38 – 1.82 (m, 8H), 1.49 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$): δ = 178.66, 175.34, 175.18, 156.44, 156.30, 153.88, 81.32, 81.23, 80.34, 58.78, 58.47, 58.33, 57.44, 44.34, 43.90, 42.57, 40.41, 40.33, 32.22, 31.60, 31.22, 30.86, 28.36, 28.23, 15.99. LCMS: [M - H]$^-$ 254.2. Anal. Calcd for $C_{13}H_{21}NO_4$: C, 61.16; H, 8.29; N, 5.49. Found: C, 61.34; H, 8.19; N, 5.43.

4,4-Dimethoxy-2,2-dimethylbutanenitrile (2b)

Yield: 132 g, 71% (from 81 g of **1b**). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.63 (t, J = 5.5 Hz, 1H), 3.39 (s, 6H), 1.85 (d, J = 5.6 Hz, 2H), 1.41 (s, 6H). ^{13}C NMR (126 MHz, DMSO-d_6): δ = 124.80, 101.66, 52.63, 41.76, 29.32, 26.53. GCMS: 126.0 [M-OCH_3]$^+$. Anal. Calcd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 61.01; H, 9.70; N, 9.05.

4,4-Dimethoxy-2,2-dimethylbutan-1-amine (3b)

Yield from **2b**: 81 g, 61%. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.42 (t, J = 5.1 Hz, 1H), 3.28 (s, 6H), 2.42 (s, 2H), 1.51 (d, J = 5.1 Hz, 2H), 0.87 (s, 6H). ^{13}C NMR (126 MHz, DMSO-d_6): δ = 102.27, 52.62, 51.96, 40.87, 33.32, 25.16. LCMS: [M + H – CH_3OH]$^+$ 130.2. Anal. Calcd for $C_8H_{19}NO_2$: C, 59.59; H, 11.88; N, 8.69. Found: C, 59.43; H, 11.95; N, 8.78.

4,4-Dimethylpyrrolidine-2-carboxylic acid hydrochloride (6b)

Yield from **7b**: 43 g, 0.24 mol, 93%. Brown powder. Mp 188−190 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.75 (s, 1H), 8.85 (s, 1H), 4.35 (s, 1H), 2.96 (q, J = 11.2 Hz, 2H), 2.12 (dd, J = 12.9, 8.6 Hz, 1H), 1.83 (dd, J = 12.9, 9.0 Hz, 1H), 1.09 (s, 3H), 1.06 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6): δ = 170.58, 58.09, 56.40, 41.86, 38.56, 25.85. LCMS: [M - Cl]$^+$ 144.2. Anal. Calcd for $C_7H_{14}ClNO_2$: C, 46.80; H, 7.86; N, 7.80. Found: C, 47.03; H, 7.91; N, 7.72.

1-(*tert*-Butoxycarbonyl)-4,4-dimethylpyrrolidine-2-carboxylic acid (7b)

4 Steps yield from **3b**: 64 g, 0.27 mol, 52%. Brown crystalline powder. Mp 94−97 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.20 (s, 1H), 4.33 (dt, J = 40.1, 8.1 Hz, 1H), 3.41 – 3.11 (m, 2H), 2.13 – 1.76 (m, 2H), 1.54 – 1.36 (m, 9H), 1.22 – 1.10 (m, 3H), 1.07 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 178.60, 175.14, 156.14, 153.44, 80.88, 79.93, 59.26, 58.68, 58.40, 58.33, 43.83, 41.71, 37.50, 37.21, 27.89, 27.79, 25.85, 25.41. LCMS: [M - H]$^-$ 242.0. Anal. Calcd for $C_{12}H_{21}NO_4$: C, 59.24; H, 8.70; N, 5.76. Found: C, 59.39; H, 8.63; N, 5.87.

1-(2,2-Dimethoxyethyl)cyclopentane-1-carbonitrile (2c)

Yield: 165 g, 83% (from 121 g of **1c**). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.64 (t, J = 5.5 Hz, 1H), 3.40 (s, 6H), 2.24 – 2.14 (m, 2H), 1.92 (d, J = 5.6 Hz, 2H), 1.90

– 1.82 (m, 2H), 1.81 – 1.72 (m, 2H), 1.72 – 1.63 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6): δ = 124.54, 102.42, 52.89, 37.70, 23.11. LCMS: $[M - CH_3O]^+$ 152.1. Anal. Calcd for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35; N, 7.64. Found: C, 65.37; H, 9.44; N, 7.80.

(1-(2,2-Dimethoxyethyl)cyclopentyl)methanamine (3c)

Yield from **2c**: 161 g, 82%. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.36 (t, J = 4.9 Hz, 1H), 3.29 (s, 6H), 2.46 (s, 2H), 1.64 (d, J = 5.0 Hz, 2H), 1.61 – 1.53 (m, 5H), 1.44 – 1.32 (m, 5H). ^{13}C NMR (101 MHz, DMSO-d_6): δ = 103.42, 103.18, 52.80, 48.85, 47.43, 45.65, 45.22, 35.66, 35.32, 24.66, 24.59. LCMS: $[M + H]^+$ 188.2. Anal. Calcd for $C_{10}H_{21}NO_2$: C, 64.13; H, 11.30; N, 7.48. Found: C, 64.22; H, 11.25; N, 7.59.

2-Azaspiro[4.4]nonane-3-carboxylic acid hydrochloride (6c)

Yield from **7c**: 100 g, 0.49 mol, 96%. Light-brown powder. Mp 181−183 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.68 (s, 1H), 8.81 (s, 1H), 4.30 (s, 1H), 3.06 (q, J = 11.3 Hz, 2H), 2.21 (dd, J = 12.9, 8.4 Hz, 1H), 1.93 (dd, J = 12.8, 8.6 Hz, 1H), 1.71 – 1.45 (m, 8H). ^{13}C NMR (126 MHz, DMSO-d_6): δ = 170.50, 58.23, 54.78, 49.30, 36.25, 35.77, 23.99. LCMS: $[M - Cl]^+$ 170.2. Anal. Calcd for $C_9H_{16}ClNO_2$: C, 52.56; H, 7.84; N, 6.81. Found: C, 52.64; H, 7.92; N, 6.70.

2-(*tert*-Butoxycarbonyl)-2-azaspiro[4.4]nonane-3-carboxylic acid (7c)

4 Steps yield from **3c**: 137 g, 0.51 mol, 59%. Brown crystalline powder. Mp 100−102 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.46 (s, 1H), 4.30 (dt, J = 45.6, 7.7 Hz, 1H), 3.47 – 3.18 (m, 2H), 2.26 – 1.90 (m, 2H), 1.78 – 1.36 (m, 17H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 179.12, 175.64, 156.47, 153.87, 81.31, 80.36, 59.29, 59.04, 58.31, 57.38, 49.05, 48.72, 42.58, 40.46, 37.42, 37.22, 36.08, 35.90, 28.37, 28.24, 24.74, 24.69, 24.56. LCMS: $[M - H]^-$ 268.0. Anal. Calcd for $C_{14}H_{23}NO_4$: C, 62.43; H, 8.61; N, 5.20. Found: C, 62.56; H, 8.70; N, 5.11.

1-(2,2-Dimethoxyethyl)cyclohexane-1-carbonitrile (2d)

Yield: 134 g, 85% (from 87 g of **1d**). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.71 – 4.64 (m, 1H), 3.38 (s, 6H), 2.04 (d, J = 13.3 Hz, 2H), 1.84 (dd, J = 5.5, 1.3 Hz, 2H), 1.77 – 1.59 (m, 5H), 1.30 (td, J = 12.8, 4.1 Hz, 2H), 1.23 – 1.13 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6): δ = 123.51, 101.89, 53.17, 42.20, 36.31, 35.40, 25.07, 22.99. GCMS: 166.0 $[M\text{-}OCH_3]^+$. Anal. Calcd for $C_{11}H_{19}NO_2$: C, 66.97; H, 9.71; N, 7.10. Found: C, 67.08; H, 9.76; N, 7.01.

(1-(2,2-Dimethoxyethyl)cyclohexyl)methanamine (3d)

Yield from **2d**: 115 g, 83%. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.40 (t, J = 5.0 Hz, 1H), 3.28 (s, 6H), 2.50 (s, 2H), 1.58 (d, J = 5.0 Hz, 2H), 1.44 – 1.23 (m, 12H). ^{13}C NMR (126 MHz, DMSO-d_6): δ = 102.48, 52.73, 48.62, 37.95, 35.81, 33.89, 26.47, 21.59. LCMS: $[M + H]^+$ 202.2. Anal. Calcd for $C_{11}H_{23}NO_2$: C, 65.63; H, 11.52; N, 6.96. Found: C, 65.38; H, 11.48; N, 7.17.

2-Azaspiro[4.5]decane-3-carboxylic acid hydrochloride (6d)

Yield from **7d**: 72 g, 0.33 mol, 93%. Beige powder. Mp 172−175 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.34 (s, 1H), 8.90 (s, 1H), 4.37 (s, 1H), 3.01 (q, J = 11.7 Hz, 2H), 2.19 (dd, J = 13.2, 8.7 Hz, 1H), 1.80 (dd, J = 13.2, 8.9 Hz, 1H), 1.54 – 1.26 (m, 10H). ^{13}C

NMR (126 MHz, DMSO-d_6): δ = 171.06, 58.09, 54.73, 42.61, 35.65, 34.81, 25.56, 23.36, 23.01. LCMS: $[M - Cl]^+$ 184.0. Anal. Calcd for $C_{10}H_{18}ClNO_2$: C, 54.67; H, 8.26; N, 6.38. Found: C, 54.54; H, 8.33; N, 6.49.

2-(*tert*-Butoxycarbonyl)-2-azaspiro[4.5]decane-3-carboxylic acid (7d)

4 Steps yield from **3d**: 99 g, 0.35 mol, 62%. Light-brown powder. Mp 100−103 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.47 (s, 1H), 4.07 (q, J = 8.0, 7.3 Hz, 1H), 3.38 – 3.23 (m, 2H), 3.01 (t, J = 11.6 Hz, 1H), 2.14 (dd, J = 13.0, 7.7 Hz, 1H), 1.58 (dt, J = 13.7, 7.0 Hz, 1H), 1.51 – 1.25 (m, 18H). ^{13}C NMR (151 MHz, DMSO-d_6): δ = 174.89, 174.40, 154.24, 153.65, 79.19, 79.14, 58.29, 58.11, 42.14, 41.26, 35.81, 35.62, 34.98, 34.79, 28.58, 28.36, 26.01, 25.97, 23.64, 23.51, 23.07. LCMS: $[M - H]^-$ 282.2. Anal. Calcd for $C_{15}H_{25}NO_4$: C, 63.58; H, 8.89; N, 4.94. Found: C, 63.67; H, 8.94; N, 5.05.

1-(2,2-Dimethoxyethyl)-4,4-difluorocyclohexane-1-carbonitrile (2e)

Yield: 26.3 g, 75% (from 21.9 g of **1e**). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.67 (t, J = 5.5 Hz, 1H), 3.39 (s, 6H), 2.19 – 2.08 (m, 6H), 1.90 (d, J = 5.6 Hz, 2H), 1.72 – 1.63 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6): δ = 121.72, 101.48, 52.82, 34.40, 31.29, 31.22, 30.28 ($^2J_{CF}$ = 25 Hz). GCMS: 202.0 $[M-OCH_3]^+$. Anal. Calcd for $C_{11}H_{17}F_2NO_2$: C, 56.64; H, 7.35; N, 6.00. Found: C, 56.84; H, 7.56; N, 5.86.

(1-(2,2-Dimethoxyethyl)-4,4-difluorocyclohexyl)methanamine (3e)

Yield from **2e**: 20.6 g, 77%. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.41 (t, J = 5.0 Hz, 1H), 3.30 (s, 6H), 2.57 (s, 2H), 1.86 (tt, J = 13.5, 6.5 Hz, 5H), 1.67 – 1.59 (m, 3H), 1.51 (t, J = 6.4 Hz, 4H). ^{13}C NMR (126 MHz, DMSO-d_6): δ = 124.40 ($^1J_{CF}$ = 241 Hz), 101.91, 52.38, 46.52, 36.52, 34.58, 29.44 ($^3J_{CF}$ = 5 Hz), 29.15 ($^2J_{CF}$ = 23 Hz). LCMS: $[M + H]^+$ 238.2. Anal. Calcd for $C_{11}H_{21}F_2NO_2$: C, 55.68; H, 8.92; N, 5.90. Found: C, 55.84; H, 8.81; N, 6.03.

8,8-Difluoro-2-azaspiro[4.5]decane-3-carboxylic acid hydrochloride (6e)

Yield form **7e**: 10 g, 0.040 mol, 91%. White powder. Mp 240−245 °C (decomp.). ^{1}H NMR (500 MHz, D_2O): δ = 4.31 (t, J = 8.5 Hz, 1H), 3.18 (q, J = 12.0 Hz, 2H), 2.31 (dd, J = 13.6, 9.1 Hz, 1H), 2.02 – 1.77 (m, 5H), 1.67 – 1.50 (m, 4H). ^{13}C NMR (151 MHz, DMSO-d_6): δ = 170.83, 124.08 (t, $^1J_{CF}$ = 242 Hz), 58.15, 53.78, 41.50, 38.43, 31.77, 31.05 (t, $^2J_{CF}$ = 24 Hz), 30.86 (t, $^3J_{CF}$ = 5 Hz), 30.67 (t, $^2J_{CF}$ = 24 Hz). ^{19}F NMR (376 MHz, D_2O): δ = -96.46. LCMS: $[M - H]^-$ 218.0. Anal. Calcd for $C_{10}H_{16}ClF_2NO_2$: C, 46.97; H, 6.31; N, 5.48. Found: C, 47.13; H, 6.22; N, 5.38.

2-(*tert*-Butoxycarbonyl)-8,8-difluoro-2-azaspiro[4.5]decane-3-carboxylic acid (7e)

4 Steps yield from **3e**: 13.7 g, 0.043 mol, 50%. White powder. Mp 162−165 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 12.55 (s, 1H), 4.16 – 4.02 (m, 1H), 3.37 – 3.31 (m, 1H), 3.19 – 3.04 (m, 1H), 2.29 – 2.19 (m, 1H), 1.99 – 1.76 (m, 4H), 1.71 – 1.47 (m, 5H), 1.42 – 1.26 (m, 9H). ^{13}C NMR (126 MHz, DMSO-d_6): δ = 174.30, 173.80, 153.66, 153.09, 123.91 (t, $^1J_{CF}$ = 241 Hz), 78.86, 78.79, 57.85, 57.66, 56.03, 55.45, 40.50, 40.37, 38.47, 31.18 (t, $^3J_{CF}$ = 5 Hz), 31.01 (t, $^3J_{CF}$ = 5 Hz), 30.91, 30.81, 30.72, 30.62, 30.57, 30.53, 30.41, 30.36, 30.22, 30.03, 28.06, 27.85. ^{19}F NMR (376 MHz, D_2O): δ = -95.37. LCMS:

$[M - H]^-$ 318.2. Anal. Calcd for $C_{15}H_{23}F_2NO_4$: C, 56.42; H, 7.26; N, 4.39. Found: C, 56.56; H, 7.20; N, 4.50.

4-(2,2-Dimethoxyethyl)tetrahydro-2*H*-pyran-4-carbonitrile (2f)

Yield: 163 g, 82% (from 112 g of **1f**). Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.68 (t, *J* = 5.6 Hz, 1H), 3.92 (dd, *J* = 12.5, 4.3 Hz, 2H), 3.72 (t, *J* = 12.2 Hz, 2H), 3.37 (s, 6H), 1.93 (d, *J* = 13.7 Hz, 2H), 1.87 (d, *J* = 5.4 Hz, 2H), 1.65 (td, *J* = 13.1, 4.5 Hz, 2H). ^{13}C NMR (126 MHz, DMSO-d_6): δ = 122.24, 101.17, 63.72, 52.72, 41.19, 34.71, 33.67. GCMS: 168.0 $[M\text{-}OCH_3]^+$. Anal. Calcd for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.37; H, 8.55; N, 7.11.

(4-(2,2-Dimethoxyethyl)tetrahydro-2*H*-pyran-4-yl)methanamine (3f)

Yield from **2f**: 136 g, 80%. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.43 (t, *J* = 5.0 Hz, 1H), 3.70 – 3.58 (m, 4H), 3.29 (s, 5H), 2.62 (s, 2H), 1.70 (d, *J* = 5.0 Hz, 2H), 1.45 (t, *J* = 5.5 Hz, 4H), 1.34 (s, 2H). ^{13}C NMR (126 MHz, DMSO-d_6): δ = 101.78, 62.66, 52.30, 47.43, 37.18, 33.50, 33.41. LCMS: $[M + H]^+$ 204.2. Anal. Calcd for $C_{10}H_{21}NO_3$: C, 59.09; H, 10.41; N, 6.89. Found: C, 59.20; H, 10.45; N, 6.81.

8-Oxa-2-azaspiro[4.5]decane-3-carboxylic acid hydrochloride (6f)

Yield from **7f**: 70 g, 0.32 mol, 95%. Light-brown powder. Mp 220−223 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.68 (s, 1H), 9.00 (s, 1H), 4.38 (t, *J* = 8.9 Hz, 1H), 3.64 – 3.43 (m, 4H), 3.10 (s, 2H), 2.31 (dd, *J* = 13.2, 8.5 Hz, 1H), 1.87 (dd, *J* = 13.1, 9.1 Hz, 1H), 1.67 – 1.43 (m, 4H). ^{13}C NMR (151 MHz, DMSO-d_6): δ = 170.85, 64.61, 64.39, 57.94, 54.32, 40.48, 39.20, 35.56, 34.87. LCMS: $[M - Cl]^+$ 186.2. Anal. Calcd for $C_9H_{16}ClNO_3$: C, 48.76; H, 7.28; N, 6.32. Found: C, 48.92; H, 7.23; N, 6.20.

2-(*tert*-Butoxycarbonyl)-8-oxa-2-azaspiro[4.5]decane-3-carboxylic acid (7f)

4 Steps yield from **3f**: 94 g, 0.33 mol, 51%. Beige powder. Mp 176−179 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.87 (s, 1H), 4.33 (dt, *J* = 44.1, 8.2 Hz, 1H), 3.82 – 3.25 (m, 6H), 2.33 – 1.80 (m, 2H), 1.63 (dt, *J* = 11.1, 5.1 Hz, 2H), 1.56 (t, *J* = 5.4 Hz, 2H), 1.52 – 1.39 (m, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 177.81, 174.46, 156.12, 153.37, 81.33, 80.15, 64.84, 64.63, 64.48, 57.88, 57.33, 56.54, 55.06, 41.51, 39.15, 38.75, 38.45, 35.13, 34.93, 34.68, 34.59, 27.90, 27.77. LCMS: $[M - H]^-$ 284.2. Anal. Calcd for $C_{14}H_{23}NO_5$: C, 58.93; H, 8.13; N, 4.91. Found: C, 59.07; H, 8.08; N, 4.80.

4-(2,2-Dimethoxyethyl)tetrahydro-2*H*-thiopyran-4-carbonitrile (2g)

Yield: 108 g, 73% (from 86 g of **1g**). Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.66 (t, *J* = 5.5 Hz, 1H), 3.36 (s, 6H), 3.02 (t, *J* = 13.3 Hz, 2H), 2.56 (d, *J* = 14.3 Hz, 2H), 2.30 (d, *J* = 12.6 Hz, 2H), 1.85 (d, *J* = 5.4 Hz, 2H), 1.69 (td, *J* = 13.2, 3.4 Hz, 2H). ^{13}C NMR (126 MHz, DMSO-d_6): δ = 122.24, 121.88, 101.17, 101.05, 63.73, 52.72, 41.54, 41.19, 35.60, 35.57, 34.71, 33.67, 24.21. GCMS: $[M]^{+\bullet}$ 215.0. Anal. Calcd for $C_{10}H_{17}NO_2S$: C, 55.78; H, 7.96; N, 6.51. Found: C, 55.96; H, 7.91; N, 6.58.

(4-(2,2-Dimethoxyethyl)tetrahydro-2*H*-thiopyran-4-yl)methanamine (3g)

Yield from **2g**: 71 g, 65%. Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.45 (t, J = 5.1 Hz, 1H), 3.32 (s, 6H), 2.70 – 2.53 (m, 6H), 1.84 – 1.63 (m, 8H). LCMS: $[M + H]^+$ 220.2. Anal. Calcd for $C_{10}H_{21}NO_2S$: C, 54.76; H, 9.65; N, 6.39. Found: C, 54.89; H, 9.55; N, 6.52.

8-Thia-2-azaspiro[4.5]decane-3-carboxylic acid hydrochloride (6g)

Yield from **7g**: 40 g, 0.17 mol, 92%. White powder. Mp 234−237°C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.63 (s, 1H), 8.99 (s, 1H), 4.36 (t, J = 8.9 Hz, 1H), 3.12 – 2.97 (m, 2H), 2.66 – 2.51 (m, 4H), 2.25 (dd, J = 13.3, 8.6 Hz, 1H), 1.86 – 1.65 (m, 5H). ^{13}C NMR (151 MHz, DMSO-d_6): δ = 170.83, 57.96, 54.49, 41.95, 39.34, 36.59, 35.57, 24.99, 24.68. LCMS: $[M - Cl]^+$ 202.2. Anal. Calcd for $C_9H_{16}ClNO_2S$: C, 45.47; H, 6.78; N, 5.89. Found: C, 45.37; H, 6.70; N, 5.98.

2-(*tert*-Butoxycarbonyl)-8-thia-2-azaspiro[4.5]decane-3-carboxylic acid (7g)

4 Steps yield from **3g**: 54 g, 0.18 mol, 57%. White powder. Mp 169−171 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.26 (s, 1H), 4.31 (dt, J = 41.8, 8.3 Hz, 1H), 3.45 (dd, J = 79.3, 10.8 Hz, 1H), 3.18 (t, J = 11.0 Hz, 1H), 2.74 – 2.51 (m, 4H), 2.30 – 1.67 (m, 6H), 1.54 – 1.35 (m, 9H). ^{13}C NMR (151 MHz, $CDCl_3$): δ = 178.88, 175.29, 156.57, 153.79, 81.82, 80.68, 58.35, 57.81, 57.33, 55.89, 41.66, 41.11, 40.73, 38.63, 36.89, 36.18, 36.01, 35.47, 28.36, 28.22, 25.64, 25.28, 25.13. LCMS: $[M - H]^-$ 300.2. Anal. Calcd for $C_{14}H_{23}NO_4S$: C, 55.79; H, 7.69; N, 4.65. Found: C, 55.97; H, 7.58; N, 4.59.

8-Thia-2-azaspiro[4.5]decane-3-carboxylic acid 8,8-dioxide hydrochloride (6h)

Yield from **7h**: 32 g, 0.12 mol, 89%. Light-brown powder. Mp 215−217 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 13.99 (s, 1H), 10.63 (s, 1H), 9.06 (s, 1H), 4.39 (t, J = 9.0 Hz, 1H), 3.19 (s, 2H), 3.14 – 3.00 (m, 4H), 2.40 (dd, J = 13.4, 8.5 Hz, 1H), 2.11 – 1.87 (m, 5H). ^{13}C NMR (126 MHz, DMSO-d_6): δ = 170.17, 57.55, 52.94, 47.73, 47.35, 40.64, 32.85, 31.74. LCMS: $[M - Cl]^+$ 234.0. Anal. Calcd for $C_9H_{16}ClNO_4S$: C, 40.08; H, 5.98; N, 5.19. Found: C, 40.21; H, 5.93; N, 5.25.

2-(*tert*-Butoxycarbonyl)-8-thia-2-azaspiro[4.5]decane-3-carboxylic acid 8,8-dioxide (7h)

Yield from **7g**: 57 g, 0.17 mol, 93%. White powder. Mp 172−175 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.22 (s, 1H), 4.50 – 4.24 (m, 1H), 3.70 – 2.91 (m, 6H), 2.45 – 1.89 (m, 6H), 1.56 – 1.37 (m, 9H). ^{13}C NMR (151 MHz, $CDCl_3$): δ = 177.16, 173.56, 156.84, 153.62, 82.85, 81.26, 58.55, 57.61, 56.68, 54.56, 48.76, 48.51, 48.45, 48.26, 40.26, 39.83, 33.14, 32.97, 32.15, 28.32, 28.19. LCMS: $[M - H]^-$ 332.0. Anal. Calcd for $C_{14}H_{23}NO_6S$: C, 50.44; H, 6.95; N, 4.20. Found: C, 50.28; H, 7.02; N, 4.31.

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