EFFICIENT MULTIGRAM SYNTHESIS OF 3,3-SPIRO-α-PROLINE CONTAINING CHIMERAS

Nikita O. Derkach,[1] Kostiantyn V. Levchenko,[1] Ievgenii A. Iermolenko,[1,2] Eugeniy N. Ostapchuk,[1,3] Dmitry A. Lega,[1,3] Valeriya G. Makhankova,[1,2] Alexander B. Rozhenko,[2,3] Dmytro M. Volochnyuk,[1,2,3] Serhiy V. Ryabukhin[1,2,3]

[1]*Enamine Ltd., 78 Winston Churchill str., 02094 Kyiv, Ukraine*

[2]*Institute of Organic Chemistry of the National Academy of Sciences of Ukraine, 5 Akademik Kukhar str., 02094 Kyiv, Ukraine*

[3]*Taras Shevchenko National University of Kyiv, 60 Volodymyrska str., 01033 Kyiv, Ukraine*

Keywords: α-proline; 3,3-spirocyclic α-prolines, heterocyclizations, medchem relevant building blocks, cyclic ketones.

Abstract

A series of novel spirocyclic α-proline building blocks for drug discovery with a spiro conjunction in position 3 of pyrrolidine was prepared by means of two convenient and practical synthetic approaches. Both alternative routes utilize simple and easily available starting materials – cyclic ketones and esters – and comprise 6- and 7-steps, respectively. The methodologies feature several advantages, including exploitation of simple organic chemistry transformations and suitability for preparation of multigram amounts of the target prolines. Approach to other valuable chemicals – spirocyclic pyroglutamic acids – is also discussed.

Introduction

Nature is the wisest synthetic chemist that have been performing in the world ever. Producing a wide range of small to complex compounds, it shows enormous ability to create molecules with unique protein binding properties and ultimate power to fulfill key roles in living organisms and environment. Owing to this, natural products have been inspiring scientists and have consistently shown to be an unrivaled point to start when it comes to drugs development.[1,2,3,4,5,6] Even though last years have been facing a decrease in interest of large pharma in naturally derived compounds, over the past three decades they have formed the basis for more than 70% of antimicrobials and 60% of chemotherapeutics that are going through clinical trials.[7] The trend is indeed dictated by unique properties of natural product pharmacophores, which inject additional hydrophilicity and increase stereochemical content in drugs of completely synthetic origins, thereby enhancing the chemical diversity available for small-molecule drug discovery.[8] It is worth mentioning that the partnership is mutual as contemporary drug discovery tools can breathe new life into natural derivatives as well. MedChem instruments allow structure of nature-inspired molecules to be rationalized and adapt to a modern medicinal chemistry paradigm. This can include the change in nature and positioning of substituents, the introduction

of peculiar functional groups and chirality centers, 3D shaping, etc., which enrich the intrinsic value and complexity of natural compounds.[9,10]

Among different groups of nature-derived structures amino acids are an essential part of the modern medicinal chemist's repertoire and the primary substances supporting biological life activities. They are responsible for vital physiological functions, being building blocks for the protein synthesis, acting as precursors for signaling molecules and energy metabolites, maintaining and regulating body development, osmotic pressure stability, and neurotransmission.[11,12] It is hardly possible to undervalue the significance of amino acids for the food and medical sectors.[13,14] In particular, they have found to display an impressive range of pharmacological activities including antitumor,[15] anti-HIV,[16] anti-fatigue effects,[17] and agents against insulin resistance and liver cirrhosis[18]. The simple and diverse structure of amino acids and advantageous physicochemical properties are commonly exploited in drug synthesis and structural modification[19,20,21] as they are a key factor for improving the pharmacological activity,[22,23] water solubility,[24,25] and cytotoxicity[26]. Another reason behind immense popularity of amino acids in drug discovery projects is availability of two orthogonal functional groups attached to a chiral center that can be readily modified by practical and commonly employed methods.[27,28] Overall, no matter what direction pharmaceutical industry will choose to proceed – low molecular APIs, medium size peptides or large proteins – it seems that there will always be a need for amino acids as they constitute a basis for each of the classes.

"Unusual" (out of the 20 canonical) amino acids is a special branch of amino acids. They are not necessarily of fully synthetic origin as naturally occurring "unusual" amino acids also exist and are formed as secondary metabolites, arisen from post-translational modifications or by other mechanisms and include hydroxylysine, MeBmt, pyrrolysine etc.[29] Nowadays, the chemical space covers more than 800 natural and thousands synthetic "unusual" amino acids[30] and this pool is constantly expanding. The tendency comes from the fact of "unusual" amino acids are gaining ever-increasing attention from MedChem community as a result of structural diversity of the side structural moiety and the presence of easily derivatized NH and CO_2H fragments within the central core. Application of such starting units in pharmaceutical campaigns brings many advantages. In particular, this approach allows for the construction of structurally diverse agents for SAR investigations, assembly of peptide-like compounds with different conformational behavior and restrictions as compared to original small molecules or peptides.[31] Recent magnificent review on the issue comprehensively sheds light on various aspects of the question with a special emphasis put on "unusual" α-amino acids that become more and more influential player in medicinal chemistry research. It also highlights structural and practical diversity of such amino acids.[32]

Among the standard amino acids pool, proline is apparently a unique one as it contains α-amino group incorporated in a five-membered cyclic framework of

pyrrolidine. This peculiar structure grants proline exclusive conformationally restricted shape that was exploited in many ways. Thus, proline and its structural variations are known for their ability to cause a reversal in the orientation of the peptide chain and to affect significantly the secondary structure of peptides and proteins.[33] Proline is being actively utilized to impart enhanced bioactivity, selectivity, water solubility and safety to natural products with poor pharmacological properties. Figure 1(A) illustrates several such cases including structurally refined anthraquinone (**I**),[34] pentacyclic triterpenoid asiatic acid (**II**)[35] and lignin podophyllotoxin (**III**)[36]. Remarkably, creation of all the hybrids improved pharmacological profile of the parent compounds with retained or improved bioactivity. The distinct influence of proline on the hybrids' structure and activity has given rise to works focusing on preparation of proline derived amino acids that were inserted into peptides to investigate their structural and biological characteristics.[37] Another case represents construction of 3,3-dimethylprolines and related derivatives to design peptidomimetics against HIV protease with enhanced metabolic stability and bioactivity.[38] A possible strategy for controlling the shape of peptide chains is to substitute 3,3-dimethylproline for proline, therefore decreasing the rate of *N*-terminal amide isomerization in peptides.[39] A representative set of approved and investigational drugs with "unusual" proline platform is exemplified in Figure 1(B). Generally, modification can affect any of proline's in-ring carbons (including condensed counterparts), thus providing derivatives that ensure perfect activity/safety profile. Compound **IV** (originated from phenylalanine predecessor for the treatment of gastrointestinal symptoms) is the odd one out within the set, owing to spirocyclic proline framework present in the molecule. In light of persisting "escape from flatland" paradigm claiming construction of architecturally complex compounds with a high level of three-dimensionality, introduction of a spiro-linkage is a powerful approach to design out-of-plane carcasses, hence adjusting molecular shape to reach enhanced receptor/ligand complementarity. Considering proline-based frameworks to be prominent scaffolds in MedChem investigations, installation of a strained spiro conjunction may allow the engineering of favorable protein-ligand interactions not possible for a much flatter monocyclic proline ring, and thus to improve selectivity and mitigate off-target outcomes.

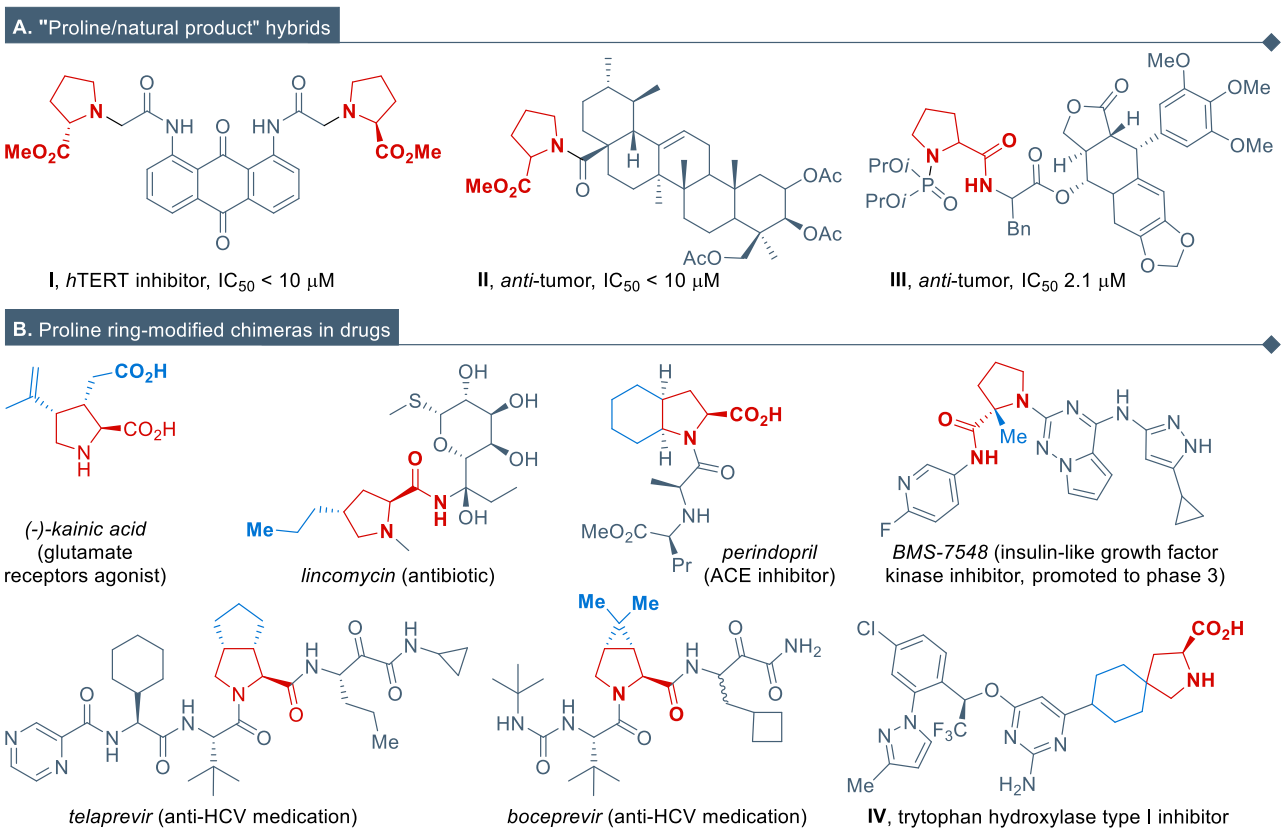


Figure 1. Overview of proline based pharmacophores

As a part of our ongoing efforts on design and synthesis of advanced building blocks for MedChem projects, our research group has developed several practical multigram approaches toward α- and β-spirocyclic pyrrolidines from readily available starting materials.[40],[41],[42] Proceeding further we were looking for new unexplored areas of chemical space in the quest to provide more sophisticated platforms for innovative drug molecules. Driven by all the beneficial effects of proline core mentioned above, we have focused our efforts on proline chimeras with a spirocyclic moiety placed in different positions with respect to the carboxyl function. Thereby, in this particular paper, we are describing our synthetic endeavors towards convenient multigram preparation of prolines with spiro conjunction in β position (Figure 2). Apart from the synthetic idea of creating new 3D shaped low-molecular scaffolds, such a spiro fusion may have other utility consequences, e.g. making molecule more stable against enzymatic degradation fate as a result of the 'umbrella' effect of the orthogonal spiro fragment.

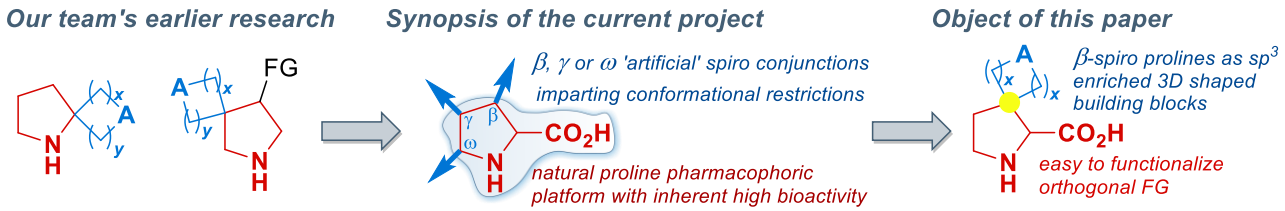


Figure 2. Evolution of our research of spiro pyrrolidines

After scanning the infospace for the related results, we were surprised to notice that despite the apparent simplicity of the target compounds and the immense number of works published with the key term "spiro" (more than 90,000 hits,

including 5,000–6,000 publications per year since 2010, according to the Reaxys® database[43]), there did not seem to be many relevant results for the synthesis of 3-spiro fused prolines (Figure 3). Thus, historically first were methods relying on radical processes. One of them included intramolecular cyclization of glycine-derived free radicals[44,45] (Figure 2, A) and another paper communicated the SET-induced photocyclization reactions of β-(aminoethyl)cyclohexenones[46,47] (Figure 2, B). However, these approaches are hardly called preparative because of low product yields and lack of selectivity. Alternative 9-step route towards a proline analog with β-spiro linked cyclopropyl moiety was proposed by *Tandon et al.* during the study of substrate specificity of human prolyl-4-hydroxylase. This multistep protocol exploited 3-hydroxyprolinol as the starting compound and utilized non-conventional reagents and conditions affording the target compound with a moderate yield (Figure 2, C).[48] 1,3-Dipolar cycloaddition seems to be the most attractive approaches existing so far. The method was elaborated and shared in the works by *Jones et al.*[49] and *Deng et al.*[50] Both studies lean on metal supported 1,3-dipolar cycloaddition reactions between ring-containing exocyclic alkenes as dipolarophiles and imines derived from α-amino acid esters, thus affording spirocycles in 40-99% yield (Figure 2, D). Some available methods to the target compounds utilize a ready-made spirocyclic core rather than a(mono)cyclic precursors Thus, in the patent[51] carboxamide group was placed in 5-azaspiro[2.4]heptane *via* organometallic mediated introduction of aldehyde followed by oxidation. Similar derivative was obtained in another patent starting from a 3-oxo proline ester through *Horner-Wittig→Simmons–Smith* reactions sequence.[52]

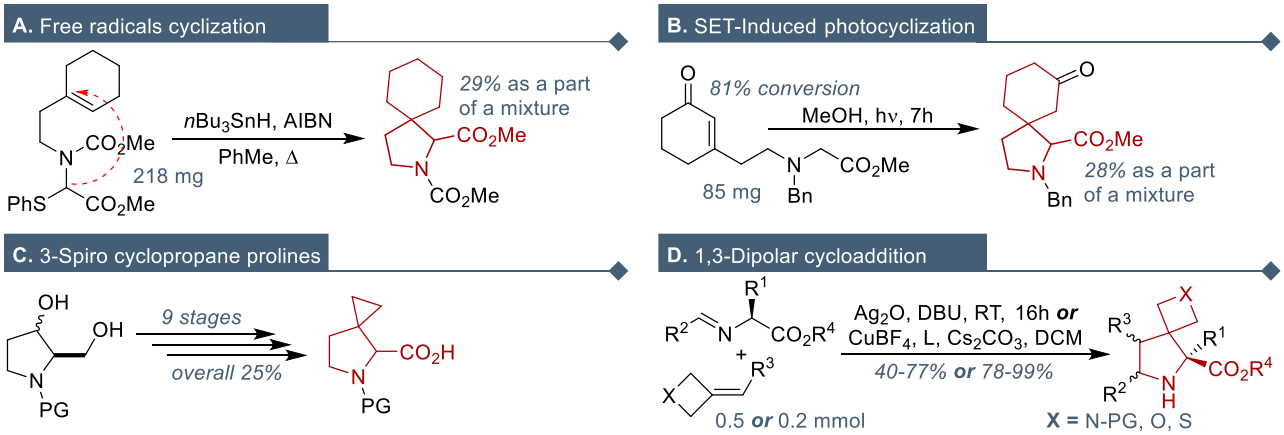


Figure 3. Approaches to 3-spiro proline platform

It is quite clear that the aforementioned methods have intrinsic shortcomings. The highlighted strategies are hardly appropriate when it comes to multigram and cost-effective synthesis of building blocks, in particular, as a result of the use of uncommon or hazardous reagents and/or catalysts, multistep reaction sequences, and/or limited substrate scope. Consequently, aiming to bring easy access to these practical derivatives herein we have turned our efforts to search for a strategy making use of readily available starting compounds, convenient synthetic steps and having broad substrate scope. These aspects are crucial for modern medicinal chemistry requiring new molecular entities to be synthesized from inexpensive and readily

available starting materials in a small number of steps with high yields. Figure 4 overviews and reflects distinctive characteristics of the present work. In brief, for preparation of the target spirocyclic chimeras we chose protocol that relies on building up proline ring moiety upon cyclic ketone (Route A) or methyl carboxylate platforms (Route B). Although not being trendy one-stage operations, both routes include reasonable number of steps, routine organic chemistry transformations and reagents, and good to excellent yields furnishing spiro prolines.

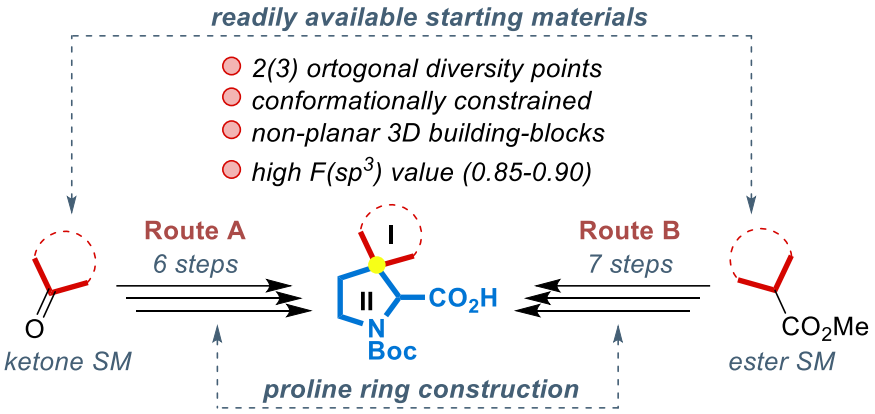


Figure 4. Hallmarks of the present work

Results and discussion

Structural peculiarities and spatial arrangement of components in a spirocyclic framework offer a conformationally rigid structure with a clearly specified vectorization along three spatial axes. This advantageous feature of spiro-built molecular carcasses has made them popular in MedChem research programs as we have stated above. However, so attractive density and rigidity simultaneously make spiro compounds fairly challenging targets for synthetic chemists. As a matter of fact, assembly of a spiro conjunction has been acknowledged to be among the trickiest operations in organic chemistry protocols.[53,54] In order to conquer the difficulty several practical methods have been developed relying on 1,3-dipolar cycloaddition reactions.[40,41] As regards 3-spirocyclic proline chimeras such a cycloaddition enables simultaneous one-step construction of a spiro framework and introduction of the carboxyl function (Figure 3, D). However, though the yields are moderate to high, and the route is concise, compounds prepared by the method are overloaded with substituents that significantly reduces their attractiveness as building blocks. At the same time "old-fashioned" stepwise approach to spirocycles is still a viable way to take advantage of and to efficiently supply those molecular structures.[42] It commonly leans on forming a tetrasubstituted prespiro-carbon prior to the cyclization step yielding spirocycles, and the strategy can be realized as a cascade process.[55,56] This way may utilize well-established organic reactions and features high flexibility, thus mostly eliminates a drawback of employing peculiar reagents and catalysts. Thereby, we chose step-by-step strategy to bring a practically useful preparation of a series of poorly documented 3-spirocyclic α-prolines. Among two principal possibilities of what initial compound to start from, we decided to use ring **I** derivatives (Figure 4) as a

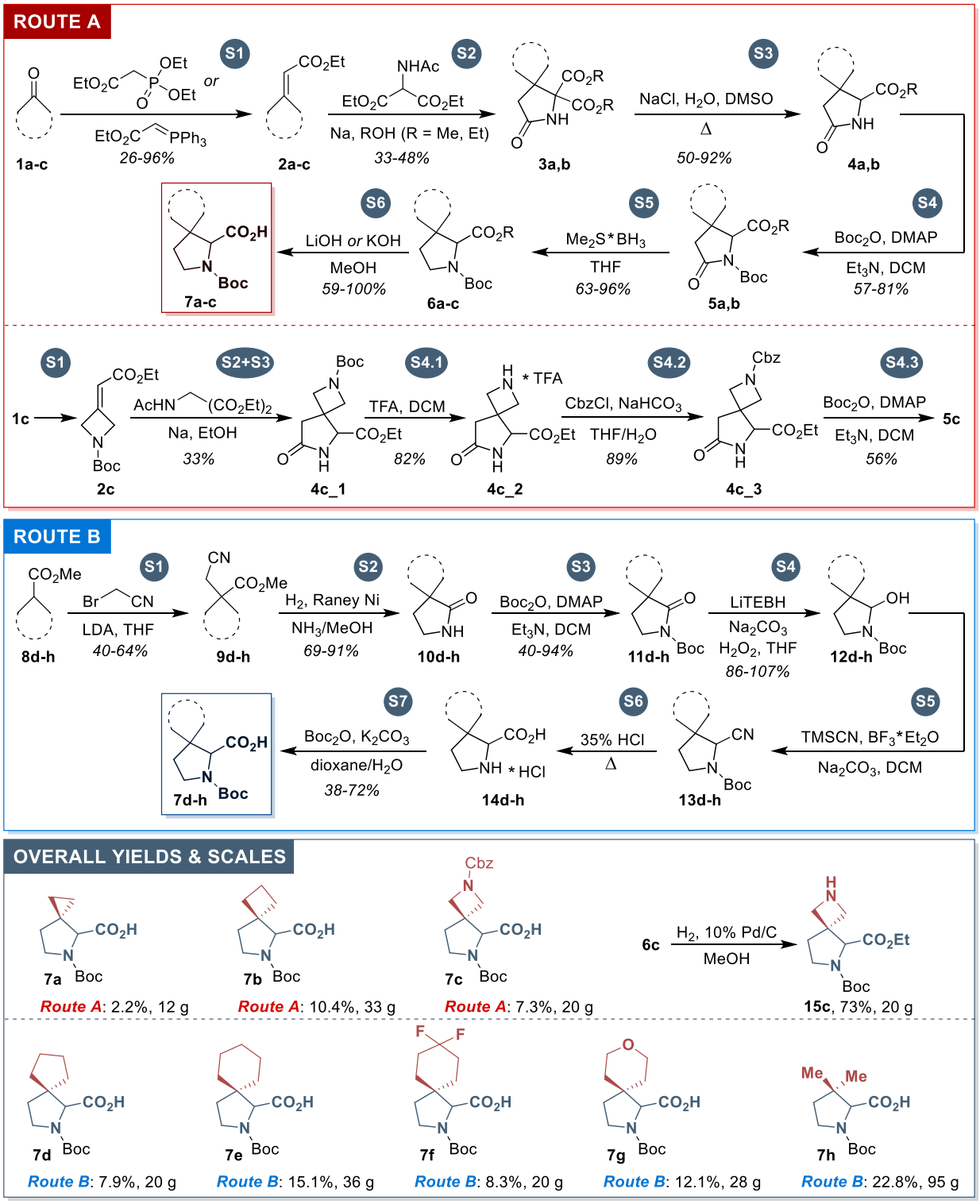
platform for the construction of proline core **II**. This is justified by easy expanding a range of cores **I** to low functionalized, e.g. carbocyclic ones.

While designing different synthetic sequences toward the target spiro prolines, we have firstly opted for cyclic ketones as starting compounds, which are versatile C1 electrophiles and readily available both commercially and synthetically. The elaborated strategy included 6 simple stages and depicted in Figure 5 (*Route A*). Suitability of this synthetic avenue for our purposes was firstly examined on cyclobutanone. The first stage (S1), we commenced from, implied introducing a two-carbon moiety *via* interaction of cyclobutanone (**1b**) with triethyl phosphonoacetate under Horner-Wadsworth-Emmons reaction conditions affording exocyclic alkene **2b** with the double bond activated by electron accepting ester function. The presence of the conjugated acrylate fragment made it previously possible to use similar alkenes as precursors in [3+2] cycloadditions with 1,3-dipoles.[40,50] Aiming to attain the desired topology, at S2 step alkene **2b** reacted with 2-aminomalonic ester derivative under basic conditions. Consecutive Michael addition and intramolecular lactamization furnished a principal backbone of the target spiro proline – pyrrolidone **3b**. This stage requires a comment. Crude diester **3b** was contaminated with the corresponding monoester and the ration was ~60:40 with the diester predominating. This mixture can be promoted to the next stage without purification, as the monoester does not interfere with the following transformation. Otherwise, the diester is also accessible as an individual compound after a purification step. Regardless of purity of the starting compound, a redundant ester group was subsequently removed from the molecule of **3b** at S3 step by means of Krapcho decarboxylation leading to monoester **4b**. This way of treating diester **3b** allowed to cleave only one of the two ester groups and keep another one intact, in contrast to the apparent alternative – base hydrolysis followed by decarboxylation sequence. Prior to reduction of the pyrrolidine part, in-ring nitrogen received Boc-protecting group (S4). A higher activity of borane dimethyl sulfide complex against a tertiary amide as compared to an ester made regioselective reduction of **5b** possible (S5), thus providing ethyl ester of spirocyclic proline **6b**. The latter was conventionally hydrolyzed to the final *N*-Boc protected spirocyclic proline chimera **7b**. The 6-stage approach is characterized by good-to-high yields of the products, convenient purification methods and handy experimental procedures that are common for the laboratory practice. One thing to point out is a weak place of the strategy being cyclization step S2 that provides the product with a moderate yield of about 33%. Unfortunately, our efforts to overcome this shortcoming did not bring some fruit so far and we are still keeping optimizing the procedure. Progress in the issue will be reported in due course. In spite of this flaw, diminishing overall yield to 10.4%, the route turned out to be workable and, what is more important, readily scalable providing 33 g of **7b** in a single synthetic run.

Having feasible synthetic protocol, we focused on expanding the substrates range and the next object we tested was cyclopropanone. Since the parent compound

is labile, we utilized its surrogate – (1-ethoxycyclopropoxy)trimethylsilane. The generation of the reactive ketone was done *in situ* under the treatment of the reaction mixture with *p*TSA. One should note that suitable partner for the ketone in this transformation was the Wittig intermediate (carbethoxymethylene)triphenylphosphorane that is a requirement of the experimental procedure. The intermediate was not produced *in situ* and applied as a ready-made substance. Notably, despite our efforts the reaction proceeded with a low yield of **2a**. The reason behind that was a high volatility of cyclopropylidene **2a** leading to substantial losses of the product while concentrating the solution at the isolation step. A slow and careful evaporation of the solvents slightly improved the situation, though the yield did not exceed 26%. The following stage S2 provided diester **3a** in a mixture with the decarboxylation product **4a** (~65:35 ratio), which can be treated similarly to the cyclobutane derivatives. Another experimental peculiarity that should be highlighted occurred at the Krapcho decarboxylation step (S3). Considering pronounced water solubility of ester **4a** the use of saturated NaCl solution is required during the extraction step in order to reach acceptable yields of the product. Otherwise, the steps S2-S6 occurred as expected, and the yields were good, though typically less than those for the cyclobutanone-derived products. Overall, the synthetic protocol showed its practicability to produce 12 g of the target proline **7a** spiro-linked with cyclopropane ring.

To further extend the synthetic and MedChem versatility of the spirocyclic products, we checked the possibility of handling *N*-Cbz protected 3-azetidinone for the generation of orthogonally protected 2,6-diazaspiro[3.4]octane-5-carboxylic acid. Access to such a proline-based building block forms the basis for further controlled functionalization on either ring nitrogen after chemoselective deprotection. In general, the elaborated protocol worked well in this case. The desire to install orthogonal protection into the final spiro proline product made us add two more stages to the synthetic route (S4.1-S4.3) thus having achieved acid **7c** with *N*-Cbz group in the azetidine portion and *N*-Boc group in the pyrrolidone part in 7.3% overall yield and 20 g scale. Such an elongation of the protocol was partially compensated by eliminating S3 stage as the construction of proline backbone and deesterification (S2+S3) were accomplished as a one-pot domino process providing spiro intermediate **4c_1**. This unexpected finding brought an advantage regarding the yield of **4c_1** being somewhat higher than the two-stage yield for **4a** and **4b**. The presence of 'naked' carboxyl function in compound **7c** enables its easy modification leaving the protected amine groups intact. In addition, we obtained amino ester **15c** *via* Pd-supported hydrogenation of intermediate **6c** that allows for specific attachment of the building block into a more complex molecule through azetidine *N*-atom.

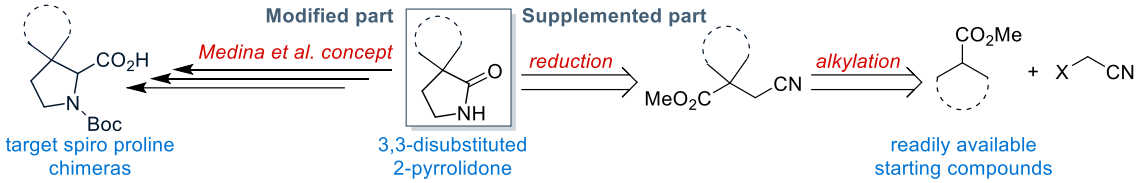


Note: (1-ethoxycyclopropoxy)trimethylsilane was used in *Route A* as a surrogate of cyclopropenone

Figure 5. Synthetic strategies, yields and scales of the target compounds

A rational advancement of the study was involvement of ever-larger and versatile cyclic ketones into the designed synthetic protocol thus creating a library of spiro prolines. However, while moving to 5-membered cyclopentanone the *Route A* turned out to be unable to furnish the desirable building blocks **7**. An obstacle emerged at the S2 stage of composing pyrrolidone framework. Thus, introducing ethyl 2-cyclopentylideneacetate (**2d**) in the reaction with the aminomalonic ester

derivative resulted in only recovery of faintly decomposed starting acrylate and no trace of the spirocyclic pyrrolidone **3d** was detected. Apparently, this outcome can be explained by a reduced electrophilicity of the conjugated double bond as the result of higher electron-pushing properties of cyclopentane as compared to the smaller rings. The same result was obtained for cyclohexane, *gem-di*-F-cyclohexane and pyrane derivatives. In light of the existed problem, we had no choice but to find a different way toward spiro prolines **7**. In search for an alternative approach, we turned our attention to a synthetic avenue communicated by *Medina et al.*[57] allowing preparation of 3,3-dimethylproline. It is based on a 7-stage route and starts from protected 3-methyl-2-pyrrolidone giving the proline derivative in 57% yield and sub-gram scale. Considering the similar topology of 3,3-dimethylproline with the desired spiro derivatives, we decided to supplement and modify the mentioned approach with the purpose of utilizing more convenient starting materials and scaling it up to multigram amounts (Scheme 1). Retro-synthetic analysis of the pyrrolidone has led us to readily available esters *via* a 2-stage synthetic sequence involving conventional reduction and alkylation. The esters were decided to use as a starting point in our alternative solution to preparation of the spiro prolines including 7 steps (Figure 5, *Route B*).



Scheme 1. Overview of the alternative route to the target spiro prolines

According to the outlined strategy, methyl cyclopentanecarboxylate (**8d**) was alkylated with bromoacetonitrile in base mediated conditions giving nitrile **9d** (61%). Raney nickel supported catalytic reduction of the nitrile was achieved in the presence of ammonia to suppress the formation of secondary/tertiary amine byproducts. The reduction with the following ring closure afforded spirocyclic 2-pyrrolidone **10d** in a cascade manner and with a high yield of 87%. After installing Boc-protection to the pyrrolidone nitrogen (S3 stage, 40% yield), lactam **11d** was supposed to transform into lactamol **12d**. Although several possible reducing approaches are known from the literature reports for this conversion (mostly DIBAL,[58] but also SMEAH[59] and $NaBH_4$[60] including Medina's work[57]) our previous experience with similar reactions evidences that lithium triethylborohydride (LiTEBH) is a reliable agent for generating lactamols from the corresponding lactams. In this case, the reaction takes a short time (usually ~0.5 hours) and proceeds cleanly without formation of over-reduction by-products. Compound **12d** was such obtained in 107% yield (crude) and promoted further without purification. Having cyclic framework of the target compound ready, the remaining challenge was introducing one-carbon moiety being precursor for the carboxyl group. This can be achieved from lactamol **12d** *via* a Lewis acid promoted *in situ* generation of *N*-acyliminium cation followed by addition of a nucleophilic

portion.[61] Thus, the interaction of **12d** with trimethylsilyl cyanide in the presence of boron trifluoride etherate provided 2-cyanopyrrolidine **13d** with 68% yield, avoiding additional *O*-methylation stage as it was reported by *Medina et al*. Subsequent acidic hydrolysis and *N*-Boc protection completed the synthetic route affording amino acid **7d**. Remarkably, all stages of the strategy were easily scaled to multigram quantities without tangible changes in yield or purity of the products as well as specific adjustment of the reaction conditions. Following the discussed scheme, we managed to obtain 20 g of spiro proline **7d** in one run. Besides, the strategy was perfectly applicable to methyl cyclohexanecarboxylate (**8e**) used as a starting compound, and after 7 stages gave the target proline **7e** with spiro-fused cyclohexane fragment. Likewise the cyclopentane derivative, multigram protocol was successfully applied in this case as well, providing 36 g of compound **7e** in overall yield of 15%. Both cyclopentane and cyclohexane derivatives acted similarly throughout the scheme toward the target spiro prolines, though the yields for cyclohexane containing products were generally higher.

While *Route B* has showed good performance with the carbocyclic substrates **8d,e**, the following examination of functionalized esters **8**, namely methyl 4,4-difluorocyclohexanecarboxylate (**8f**) and methyl tetrahydro-2*H*-pyran-4-carboxylate (**8g**), revealed some interesting details. Thus, the stages S1-S4 proceeded with a comparable efficiency for these substrates and affected the cyclic portion in no way. At the same time, while attempting substitution of OH with CN (stage S5) we have come across an issue being the reaction product contains substantial percentage of the starting material (initially nearly 50%). Alternation of the reaction conditions (in particular, temperature mode, reaction time, and catalyst) did not eliminate the problem completely. However, a reasonable increase of the catalyst and TMSCN loads enabled us to reach 70:30 ratio of CN to OH derivatives in the isolated material. Further experiments have proved the fact that the presence of unreacted lactamol does not interfere with the subsequent steps. Another interesting detail was faced at the stage of acidic hydrolysis of CN group for *gem-di*-F derivative **13f**. The standard procedure exploiting dilute HCl did not provide an acceptable result in this case as CF_2 fragment underwent hydrolytic cleavage as well with the formation of the corresponding ketone (not isolated, observed in HPLC-MS spectra). The selectivity issue caused a significant reduction in the product yields to 15-20%. We managed to resolve the problem by using acetic acid as a reaction medium and a lower amount of HCl. In such conditions, the desired amino acid hydrochloride **14f** was isolated in ~60% yield. The final *N*-Boc protection of hydrochlorides **14f,g** did not have notable features and led to the target compounds **7f,g**. All the stages toward these derivatives were successfully scaled that made it possible to obtain 20 g of **7f** and 53 g of **7g** within a single synthetic run.

Considering the low overall yield of cyclopropane decorated spiro proline **7a** achieved in *Route A*, we shifted our focus to *Route B* to explore the possibility of

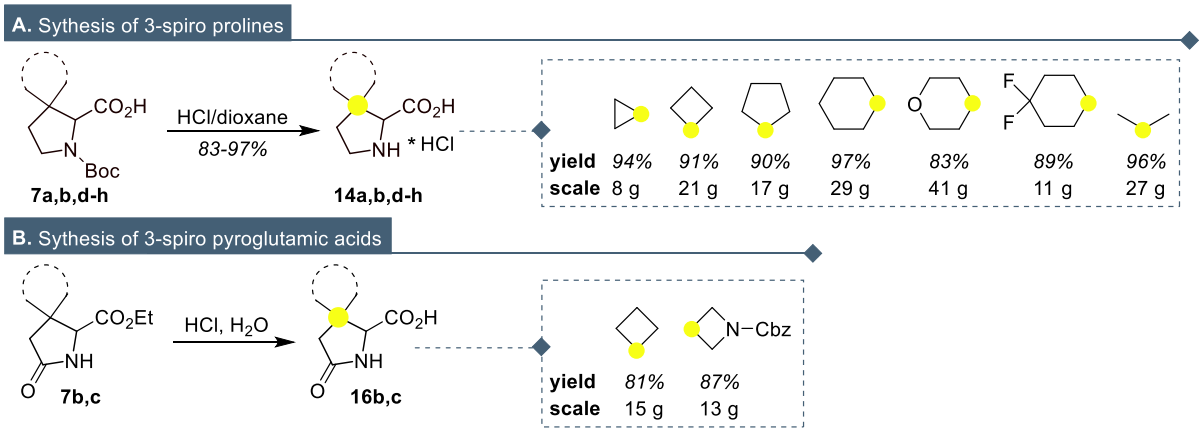
improving it. Commercially available methyl cyclopropanecarboxylate was employed as the starting compound. Unfortunately, after the prosperous alkylation step the procedure failed at the stage S2. The reason was the lability of cyclopropane ring against Raney Ni supported reduction that resulted in a mixture of products.

In the introduction part we have touched on utility of 3,3-dimethylproline molecular platform for medicinal chemistry investigations, which was also regarded as proline-valine chimera.[62] What is more, *gem-di*-Me fragment imparts enhanced metabolic stability to the molecules containing it. Besides that, inclusion of 3,3-dimethylproline derivatives in medicinal chemistry programs of pharmaceutical giants, like SmithKline Beecham Corp.[63] and AstraZeneca[64] also adds to its value. Evidently, 3,3-dimethylproline is closely related to the objects of the current study. However, as far as we know preparative approaches to this compound are scarce. The handiest preparation scheme by *Medina et al.* starts from inconvenient and inflexible *N*-TBS-protected 3-methyl-2-pyrrolidone and provides sub-gram quantities of 3,3-dimethylproline. Due to all the arguments, we decided to test applicability and effectiveness of the *Route B* for multigram preparation of the latter. For this reason, we used *in bulk* and cheap methyl isobutyrate as the starting compound. Overall, the synthetic protocol proceeded smoothly without notable peculiarities to be outlined and provided 95 g of 5,5-dimethylproline (**7h**) in 22.8% 7-stage yield. Accomplished synthesis of **7h** assumes that the way is an excellent option for the preparation of the related 3,3-disubstituted alkyl homologues including non-symmetrical ones, which are currently unknown, though definitely of MedChem interest. This research direction seems promising for us, and we are going to communicate achievements on the question in our upcoming works.

Having a developed tool for obtaining spirocyclic structures, we next decided to synthesize unprotected amino acids, as they are also widely applicable building blocks in organic and bioorganic chemistry investigations. This was achieved by simple removing Boc-group *via* treatment of the starting compounds **7** with HCl/dioxane solution affording amino acids **14** in high yields (Scheme 2, A).

Finally, we would like to discuss spiro lactams **4** as, along with the target spiro prolines **7**, they represent another captivating structural topology. In fact, they are esterified spiro analogs of pyroglutamic acid, which is a ubiquitous however scarcely investigated natural amino acid.[65] Particularly, this chemical was identified both as a free metabolite in varied living cells or as a bound one at the *N*-terminus of proteins, e.g. bacteriorhodopsin. This natural molecule is commercially available as a nootropic dietary supplement and has shown to elicit anti-diabetic activity, remarkable inhibitory property against PDE-5, ACE, urease enzymes.[66,67] Recently, a pyroglutamide derivative has been identified as a potent RORγt agonist and can be useful agent for treating psoriasis.[68] Pyroglutamic acid and its derivatives have been prepared by numerous ways including multicomponent as well as multistep approaches. However, its 3-spiro linked counterparts are nearly unknown and were

only disclosed in a couple of patents.[69,70] 3-Step approach proposed in this work and illustrated in Figure 5 (*Route A*) is a practical method to such valuable derivatives. In order to reach derivatives with free carboxyl function eligible for further convenient functionalization we performed hydrolysis of compounds **4**, thus obtaining amino acids **16** (Scheme 2, B).



Scheme 2. Synthesis of 3-spiro prolines and 3-spiro pyroglutamic acids

Conclusions

In summary, 'unusual' 3D-shaped α-amino acids have broken into modern medicinal chemistry and become its indispensable components. This tendency is a direct consequence of the growing desire to *escape from flatland*, the expanding recognition of peptides as versatile medical agents, and immense freedom in creating such molecular platforms with diverse side chains. Moreover, natural origin of α-amino acids and their inherent biomedical value may impart prominent properties to the products containing such pharmacophores. Substitution of certain amino acid residues in naturally occurring peptides is a promising way of comprehending a mechanism of their action and, what is more, limitless possibility to control their activity. Guided by all the motives, herein we reported practical protocols for the preparation of conformationally constrained α-prolines bearing spiro conjunction in position 3 of the pyrrolidine ring. Two elaborate synthetic avenues utilize readily accessible starting materials (cyclic ketones and carbo(hetero)cyclic esters) and operate routine experimental procedures without a need to use peculiar reagents. Following those approaches we were able to construct nine simple low-substituted prolines with different spiro linked cores. The protocols were adapted to preparation of multigram quantities of the target products, thus providing of up to 36 grams of prolines in a single synthetic run. Additionally, the synthetic methodology was used for efficient preparation of 95 grams of 3,3-dimethylproline, which can be regarded as a mimic of the prepared spiro products. Other value-added products the paper deals with are spirocyclic pyroglutamic acids, which are nearly unknown, though promising building blocks for MedChem purposes. These derivatives wer eobtained in good yields and large scale.

Most of the described compounds were either unknown or hard to obtain so far. With this, the work opens up access to new areas of chemical space and supports

ongoing endeavors in creation of novel potent pharmaceutical substances. We believe that its findings will be useful for a wide range of research groups from both academia and industry.

Experimental part

This section contains optimized protocols for the preparation of the compounds described throughout the paper.

All starting compounds were obtained from commercial sources and used without additional purification. All solvents were purified according to the standard procedures. All compounds known from the literature are given appropriate reference; experimental data comply with the referenced papers.

1.37 M LDA solution was prepared from interaction of *n*BuLi (1.0 equiv, 2.5 M solution in hexanes) with diisopropylamine (1.05 equiv) in THF (0.32 mL per 1 mmol of diisopropylamine) under argon 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. 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. 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.

N-Boc protected prolines **7** adopt two major rotameric conformations, what is manifested in doubling signals in ^{13}C NMR spectra.

SYNTHETIC PROCEDURES FOR THE *ROUTE A* STRATEGY EMPLOYING KETONES AS THE STARTING COMPOUNDS

5-(*tert*-Butoxycarbonyl)-5-azaspiro[2.4]heptane-4-carboxylic acid (7a)

Step 1. Synthesis of ethyl 2-cyclopropylideneacetate[71] (**2a**)

(1-Ethoxycyclopropoxy)trimethylsilane (600 g, 3.4 mol) was dissolved in benzene (9.6 L), then pTSA (393 g, 2.0 mol) was added. (Carbethoxymethylene)triphenylphosphorane (1.44 kg, 4.1 mol) was added portionwise to the mixture. After that, the reaction mixture was stirred at reflux for two days. Then the resulting mixture was cooled to room temperature and the precipitate was filtered off, benzene solution was concentrated on a rotary evaporator. Hexane was added to the residue and the mixture was filtered. The filtrate was concentrated on a rotary evaporator and the residue after evaporation

was distilled *in vacuo* to obtain ethyl 2-cyclopropylideneacetate (**2a**) (110 g, 0.88 mol, 26%).

Colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.22 (p, J = 2.0 Hz, 1H), 4.21 (q, J = 7.2 Hz, 2H), 1.45 (ddd, J = 9.8, 7.9, 2.3 Hz, 2H), 1.30 (t, J = 7.1 Hz, 3H), 1.23 (ddd, J = 10.9, 8.0, 1.7 Hz, 2H) ppm. GCMS: $[M]^{+\bullet}$ 126.1, $[M - C_2H_4]^{+\bullet}$ 98.1. Anal. Calcd for $C_7H_{10}O_2$, %: C 66.65, H 7.99. Found, %: C 56.73, H 7.94.

Step 2. Synthesis of dimethyl 6-oxo-5-azaspiro[2.4]heptane-4,4-dicarboxylate (**3a**)

Metallic sodium (15.4 g, 0.64 mol) was dissolved in dry methanol (1.2 L), then a flask with the reaction mixture was placed in an ice bath, and diethyl 2-acetamidomalonate (127 g, 0.58 mol) was added in one portion, the reaction mixture was stirred for another hour. After that ethyl 2-cyclopropylideneacetate (**2a**) (110 g, 0.88 mol) was added in one portion and the reaction mixture was refluxed for two days. then cooled to room temperature and acetic acid (42 mL, 0.7 mol) was added. The resulting mixture was concentrated on a rotary evaporator and the residue was diluted with ethyl acetate (1 L) and water (0.5 L). The organic layer was separated and the water was twice extracted with ethyl acetate, the combined organic fraction was washed with an aqueous sodium hydrogen carbonate solution, dried over sodium sulfate and concentrated *in vacuo*. The flask with the residue after evaporation was placed in an ice bath, the precipitate was filtered and washed with a small amount of diethyl ether to obtain dimethyl 6-oxo-5-azaspiro[2.4]heptane-4,4-dicarboxylate (**3a**) (64 g, 0.28 mol, 48%).

Step 3. Synthesis of methyl 6-oxo-5-azaspiro[2.4]heptane-4-carboxylate (**4a**)

Dimethyl 6-oxo-5-azaspiro[2.4]heptane-4,4-dicarboxylate (**3a**) (64 g, 0.28 mol) was dissolved in dry DMSO (200 mL), then distilled water (15.2 mL, 0.84 mol) and sodium chloride (14.3 g, 0.34 mol) were added to the reaction mixture. The reaction mixture was refluxed for 3 hours, cooled to room temperature, and poured into ethyl acetate (1.2 L). The ethyl acetate layer was separated, washed with a saturated aqueous sodium chloride solution (2×300 mL), the aqueous layer was washed with ethyl acetate (2×300 mL), the organic fractions were combined, dried over sodium sulfate and concentrated *in vacuo* to obtain methyl 6-oxo-5-azaspiro[2.4]heptane-4-carboxylate (**4a**) (24 g, 0.14 mol, 50%).

Step 4. Synthesis of 5-(tert-butyl) 4-methyl 6-oxo-5-azaspiro[2.4]heptane-4,5-dicarboxylate (**5a**)

Methyl 6-oxo-5-azaspiro[2.4]heptane-4-carboxylate (**4a**) (24 g, 0.14 mol) was dissolved in dry dichloromethane (300 mL), then triethylamine (29.6 mL, 0.21 mol) and DMAP (1.7 g, 0.01 mol) were added to the solution. Next, the reaction mixture was cooled in an ice bath and Boc_2O (36 mL, 0.15 mol) was added dropwise. Then the reaction mixture was stirred at room temperature for 16 hours, washed with 10% aqueous sodium hydrogen sulfate solution (2×200 mL), organic layer was separated

and dried over sodium sulfate and concentrated *in vacuo* to obtain 5-(*tert*-butyl) 4-methyl 6-oxo-5-azaspiro [2.4]heptane-4,5-dicarboxylate (**5a**) (24 g, 0.08 mol, 57%).

Step 5. Synthesis of 5-(tert-butyl) 4-methyl 5-azaspiro[2.4]heptane-4,5-dicarboxylate (**6a**)

5-(*tert*-Butyl) 4-methyl 6-oxo-5-azaspiro[2.4]heptane-4,5-dicarboxylate (**5a**) (24 g, 0.08 mol) was dissolved in dry THF (300 mL), the flask was placed in a water bath and borane dimethyl sulfide complex (13.4 ml, 0.142 mol) was added dropwise under argon stream at room temperature. The reaction mixture was allowed to stir for 16 hours at room temperature. Then, while cooling with an ice bath, a saturated potassium carbonate solution (49 g, 0.35 mol) was slowly added to the reaction mixture. Upon completion, the reaction mixture was poured into MTBE, the aqueous layer was separated, washed with MTBE, and the combined organic fraction was washed with brine, dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by flash chromatography (hexane/ethyl acetate 5:1) to obtain 5-(*tert*-butyl) 4-methyl 5-azaspiro[2.4]heptane-4,5-dicarboxylate (**6a**) (14 g, 0.05 mol, 63%).

Step 6. Synthesis of 5-(tert-butoxycarbonyl)-5-azaspiro[2.4]heptane-4-carboxylic acid (**7a**)

Potassium hydroxide (9.2 g, 0.16 mol) was dissolved in dry methanol (100 mL), the solution was cooled to room temperature, and a solution of 5-(*tert*-butyl) 4-methyl 5-azaspiro[2.4]heptane-4,5-dicarboxylate (**6a**) (14 g, 0.05 mol) in dry methanol (40 mL) was added in one portion. The reaction mixture was stirred at room temperature for 16 hours and then concentrated under reduced pressure. The residue was dissolved in water (300 mL) and the solution was twice washed with MTBE, acidified with sodium hydrogen sulfate (23 g, 0.19 mol), and twice extracted with ethyl acetate. MTBE fraction was separated, dried over sodium sulfate, and concentrated *in vacuo* to obtain the target 5-(*tert*-butoxycarbonyl)-5-azaspiro[2.4]heptane-4-carboxylic acid (**7a**) (12 g, 0.05 mol, 100%).

5-(*tert*-Butoxycarbonyl)-5-azaspiro[2.4]heptane-4-carboxylic acid (7a)

6 Steps yield: 12 g, 0.05 mol, 2.2%. White crystalline powder. Mp: 131−134 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.81 – 3.61 (m, 2H), 3.58 – 3.44 (m, 1H), 2.30 (dd, J = 24.8, 12.1 Hz, 1H), 1.55 – 1.34 (m, 10H), 1.03 – 0.85 (m, 1H), 0.78 – 0.56 (m, 3H), CO_2H proton is in exchange. ppm. $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$): δ 177.74, 176.66, 154.79, 153.71, 80.36, 65.26, 64.85, 46.31, 45.87, 32.98, 32.29, 28.41, 28.26, 25.56, 24.81, 15.15, 6.34, 6.16 ppm. LCMS: $[M - H]^-$ 240.2. Anal. Calcd for $C_{12}H_{19}NO_4$, %: C 59.73, H 7.94, N 5.81. Found, %: C 59.92, H 7.99, N 5.70.

6-(*tert*-Butoxycarbonyl)-6-azaspiro[3.4]octane-5-carboxylic acid (7b)

Step 1. Synthesis of ethyl 2-cyclobutylideneacetate[72] (**2b**)

Sodium hydride (60% suspension in mineral oil, 81.5 g, 2.0 mol) was suspended in dry THF (400 mL), the mixture was cooled in an ice bath, and triethyl phosphonoacetate (423 mL, 2.13 mol) was added dropwise. Upon completion the reaction mixture was stirred for 30 minutes until the bubbling ceased. After that, a

solution of cyclobutanone (130 g, 1.85 mol) in dry THF (300 mL) was added dropwise while cooling the reaction mixture with ice. Then the resulting mixture was stirred at room temperature for 16 hours. After that, THF was decanted, the remaining solid was washed with one portion of THF (500 mL) and also decanted. The combined THF fraction was concentrated under reduced pressure and the residue was purified by distillation *in vacuo* to obtain ethyl 2-cyclobutylideneacetate (164.5 g, 1.17 mol, 63%).

Colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.57 (p, J = 2.4 Hz, 1H), 4.14 (q, J = 7.2 Hz, 2H), 3.13 (t, J = 8.0 Hz, 2H), 2.83 (tt, J = 8.4, 2.0 Hz, 2H), 2.08 (p, J = 8.0 Hz, 2H), 1.26 (t, J = 7.1 Hz, 3H) ppm. GCMS: $[M]^{+\bullet}$ 140.0. Anal. Calcd for $C_8H_{12}O_2$, %: C 68.55, H 8.63. Found, %: C 68.61, H 8.68.

Step 2. Synthesis of diethyl 7-oxo-6-azaspiro[3.4]octane-5,5-dicarboxylate (**3b**)

Metallic sodium (20.66 g, 0.86 mol) was dissolved in absolute ethanol (2 L), then the solution was cooled on an ice bath, and diethyl 2-acetamidomalonate (170 g, 0.78 mol) was added in one portion. The resulting mixture was stirred for 1 hour followed by adding ethyl 2-cyclobutylideneacetate (**2b**) (164.5 g, 1.17 mol) in one portion and the reaction mixture was refluxed for 16 hours. Upon completion, the content was cooled to room temperature and acetic acid (53.7 mL, 0.94 mol) was added. The mixture was concentrated under reduced pressure and the residue was diluted with ethyl acetate (1 L) and water (1 L). The organic layer was separated, and the water layer was twice extracted with ethyl acetate. The combined organic fraction was washed with aqueous sodium hydrogen carbonate solution, dried over sodium sulfate, and concentrated *in vacuo*. The flask with residue after concentration was cooled on an ice bath, the precipitate formed was filtered off and washed with hexane to obtain diethyl 7-oxo-6-azaspiro[3.4]octane-5,5-dicarboxylate (**3b**) (71 g, 0.26 mol, 33%).

Step 3. Synthesis of ethyl 7-oxo-6-azaspiro[3.4]octane-5-carboxylate (**4b**)

Diethyl 7-oxo-6-azaspiro[3.4]octane-5,5-dicarboxylate (**3b**) (71 g, 0.26 mol) was dissolved in dry DMSO (210 mL), then distilled water (14.2 mL, 0.79 mol) and sodium chloride (18.5 g, 0.32 mol) were added and the reaction mixture was refluxed for 3 hours. Then the content was cooled to room temperature, poured into ice-cold water (600 mL) and extracted with ethyl acetate (3×600 mL). The ethyl acetate layer was separated, washed with a saturated aqueous solution of sodium chloride, dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate 2:1) to obtain ethyl 7-oxo-6-azaspiro[3.4]octane-5-carboxylate (**4b**) (47 g, 0.24 mol, 92%).

Step 4. Synthesis of 6-(tert-butyl) 5-ethyl 7-oxo-6-azaspiro[3.4]octane-5,6-dicarboxylate (**5b**)

Ethyl 7-oxo-6-azaspiro[3.4]octane-5-carboxylate (**4b**) (47 g, 0.24 mol) was dissolved in dry dichloromethane (500 mL), then triethylamine (49.8 mL, 0.36 mol) and DMAP (2.9 g, 0.024 mol) were added, the reaction mixture was cooled on an ice bath and Boc_2O (60 mL, 0.26 mol) was added dropwise. The resulting mixture was

stirred for 16 hours at room temperature, then washed with an aqueous solution of sodium hydrogen sulfate, the organic layer was separated, dried over sodium sulfate and concentrated in vacuo to obtain 6-*tert*-butyl 5-ethyl 7-oxo-6-azaspiro[3.4]octane-5,6-dicarboxylate (**5b**) (58 g, 0.195 mol, 81%).

Step 5. Synthesis of 6-(tert-butyl) 5-ethyl 6-azaspiro[3.4]octane-5,6-dicarboxylate (**6b**)

6-*tert*-Butyl 5-ethyl 7-oxo-6-azaspiro[3.4]octane-5,6-dicarboxylate (**5b**) (58 g, 0.195 mol) was dissolved in dry THF (600 mL), the flask was placed in a water bath, and borane dimethyl sulfide complex (29.6 mL, 0.312 mol) was added dropwise under argon stream. The reaction mixture was left to stir for 16 hours at room temperature. Then, while cooling with ice, a saturated solution of potassium carbonate (108 g, 0.78 mol) was slowly added to the reaction mixture. Upon completion, the reaction mixture was poured into MTBE, the aqueous layer was separated, washed with MTBE, the combined organic fraction was washed with brine, dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by flash chromatography (hexane/ethyl acetate 5:1) to obtain 6-*tert*-butyl 5-ethyl 6-azaspiro[3.4]octane-5,6-dicarboxylate (**6b**) (42 g, 0.148 mol, 76%).

Step 6. Synthesis of 6-(tert-butoxycarbonyl)-6-azaspiro[3.4]octane-5-carboxylic acid (**7b**)

Potassium hydroxide (25 g, 0.444 mol) was dissolved in dry methanol (300 mL), the content was cooled to room temperature, and a solution of 6-*tert*-butyl 5-ethyl 6-azaspiro[3.4]octane-5,6-dicarboxylate (**6b**) (42 g, 0.148 mol) in dry methanol (120 mL) was added to the reaction mixture in one portion. The content was stirred for 16 hours at room temperature and the resulting mixture was concentrated under reduced pressure. The residue was dissolved in water and the solution was twice washed with MTBE, acidified with sodium hydrogen sulfate (62.3 g, 0.52 mol), twice extracted with ethyl acetate, dried over sodium sulfate and concentrated in vacuo thus affording **7c** (33 g, 0.13 mol, 88%).

6-(*tert*-Butoxycarbonyl)-6-azaspiro[3.4]octane-5-carboxylic acid (7b)

6 Steps yield: 33 g, 0.13 mol, 10.4%. White powder. Mp: 108–111 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.18 – 4.00 (m, 1H), 3.66 – 3.46 (m, 1H), 3.40 – 3.24 (m, 1H), 2.39 – 2.20 (m, 1H), 2.14 – 1.76 (m, 7H), 1.50 – 1.36 (m, 9H) ppm, CO_2H proton is in exchange. $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$): δ 177.35, 176.13, 154.95, 153.95, 80.29, 68.19, 67.54, 48.37, 47.38, 44.67, 44.27, 35.68, 35.13, 34.40, 28.39, 28.26, 27.49, 27.30, 16.04 ppm. 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 61.03, H 8.38, N 5.40.

2-(*tert*-Butoxycarbonyl)-2-azaspiro[4.4]nonane-1-carboxylic acid (7c)

Step 1. Synthesis of tert-butyl 3-(2-ethoxy-2-oxoethylidene)azetidine-1-carboxylate[73] (**2c**)

tert-Butyl 3-oxoazetidine-1-carboxylate (120 g, 0.7 mol) was dissolved in dichloromethane (1.2 L), then (carbethoxymethylene)triphenylphosphorane (293 g,

0.85 mol) was added portionwise while cooling the flask in an ice bath. The reaction mixture was then stirred at room temperature overnight and concentrated under reduced pressure. The residue after evaporation was triturated in hexane/MTBE (4:1) mixture, triphenylphosphine oxide was filtered off and the filtrate was concentrated *in vacuo*. The residue was purified using flash chromatography (hexane/ethyl acetate 3:1) to obtain *tert*-butyl 3-(2-ethoxy-2-oxoethylidene)azetidine-1-carboxylate (**2c**) (162.5 g, 0.67 mol, 96%).

Colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.76 (p, J = 2.4 Hz, 1H), 4.84 – 4.79 (m, 2H), 4.62 – 4.56 (m, 2H), 4.17 (q, J = 7.1 Hz, 2H), 1.45 (s, 9H), 1.28 (t, J = 7.1 Hz, 3H) ppm. GCMS: $[M]^{+\bullet}$ 241.2. Anal. Calcd for $C_8H_{12}O_2$, %: C 61.56, H 8.02, N 6.42. Found, %: C 61.72, H 7.91, N 6.28.

Steps 2-3. Synthesis of 2-(tert-butyl) 5-ethyl 7-oxo-2,6-diazaspiro[3.4]octane-2,5-dicarboxylate (**4c_1**)

Metallic sodium (16.6 g, 0.67 mol) was dissolved in absolute ethanol (1.6 L), the reaction mixture was cooled in an ice bath, and diethyl 2-acetamidomalonate (133 g, 0.61 mol) was added in one portion. The resulting mixture was stirred for 1 hour, and *tert*-butyl 3-(2-ethoxy-2-oxoethylidene)azetidine-1-carboxylate (**2c**) (162.5 g, 0.67 mol) was added in one portion, and the reaction mixture was refluxed for 36 hours. Upon completion, the reaction mixture was cooled to room temperature, and acetic acid (36.8 mL, 0.64 mol) was added. The resulting content was concentrated under reduced pressure, the residue was partitioned between ethyl acetate (1 L) and water (1 L), the water layer was washed with ethyl acetate (0.5 L), and the combined organic fraction was washed with 10% sodium hydrogen carbonate solution (0.5 L) and brine (0.5 L), dried over sodium sulfate and concentrated *in vacuo*. The residue was mixed with hexane/MTBE (4:1) mixture, cooled in an ice bath, the precipitate formed was filtered off and washed with MTBE to obtain 2-(*tert*-butyl) 5-ethyl 7-oxo-2,6-diazaspiro[3.4]octane-2,5-dicarboxylate (**4c_1**) (65.5 g, 0.22 mol, 33%).

Step 4.1. Synthesis of ethyl 7-oxo-2,6-diazaspiro[3.4]octane-5-carboxylate trifluoroacetate (**4c_2**)

Ethyl 7-oxo-2,6-diazaspiro[3.4]octane-5-carboxylate (**4c_1**) (65.5 g, 0.22 mol) was dissolved in dry dichloromethane (250 mL), the reaction mixture was cooled in an ice bath, and trifluoroacetic acid (250 mL) was added dropwise. The reaction mass was stirred at room temperature overnight and concentrated under reduced pressure. The residue after evaporation was poured into MTBE and stirred for an hour. Then a precipitate of ethyl 7-oxo-2,6-diazaspiro[3.4]octane-5-carboxylate trifluoroacetate (**4c_2**) (57.3 g, 0.18 mol, 82%) was filtered off and promoted to the next synthetic step without an additional purification.

Step 4.2. Synthesis of 2-benzyl 5-ethyl 7-oxo-2,6-diazaspiro[3.4]octane-2,5-dicarboxylate (**4c_3**)

Ethyl 7-oxo-2,6-diazaspiro[3.4]octane-5-carboxylate trifluoroacetate (**4c_2**) (57.3 g, 0.18 mol) was dissolved in the THF/water mixture (570/285 mL), $NaHCO_3$ (34

g, 0.4 mol) was added in portions followed by CbzCl (31.3 mL, 0.22 mol) slowly added dropwise. The reaction mixture was stirred at room temperature overnight and then poured into ethyl acetate (600 mL). The organic layer was separated, washed with saturated sodium chloride solution, dried over sodium sulfate, and concentrated *in vacuo* to afford 2-benzyl 5-ethyl 7-oxo-2,6-diazaspiro[3.4]octane-2,5-dicarboxylate (**4c_3**) (53 g, 0.16 mol, 89%) using in the next step without purification.

Step 4.3. Synthesis of 2-benzyl 6-(tert-butyl) 5-ethyl 7-oxo-2,6-diazaspiro[3.4]octane-2,5,6-tricarboxylate (**5c**)

2-Benzyl 5-ethyl 7-oxo-2,6-diazaspiro[3.4]octane-2,5-dicarboxylate (**4c_3**) (53 g, 0.16 mol) was dissolved in dichloromethane (530 mL), then triethylamine (33.3 mL, 0.24 mol) and DMAP (1.95 g, 0.016 mol) were added, and the reaction mixture was cooled in an ice bath. Boc_2O (40.3 mL, 0.175 mol) was added dropwise and the reaction mass was left to stir at room temperature overnight. Upon completion, the reaction mixture was washed with water and 10% aqueous solution of sodium hydrogen sulfate (2x300 mL), the organic layer was dried over sodium sulfate and concentrated on a rotary evaporator. The residue was mixed with MTBE and the mixture was concentrated again under reduced pressure. After that the residue was poured with diethyl ether and the precipitate was filtered off to obtain 2-benzyl 6-*tert*-butyl 5-ethyl 7-oxo-2,6-diazaspiro[3.4]octane-2,5,6-tricarboxylate (**5c**) (46 g, 0.09 mol, 56%).

Step 5. Synthesis of 2-benzyl 6-(tert-butyl) 5-ethyl 2,6-diazaspiro[3.4]octane-2,5,6-tricarboxylate (**6c**)

2-Benzyl 6-*tert*-butyl 5-ethyl 7-oxo-2,6-diazaspiro[3.4]octane-2,5,6-tricarboxylate (**5c**) (46 g, 0.09 mol) was dissolved in dry THF (460 mL), the flask was placed in a water bath and borane dimethyl sulfide complex (22.8 mL, 0.24 mol) was added dropwise under argon flow. The reaction mixture was left to stir for 16 hours at room temperature. Upon completion, the flask was placed in an ice bath, and a saturated solution of potassium carbonate (64 g, 0.462 mol) was carefully added dropwise to the reaction mixture. The resultant mass was poured into MTBE, the aqueous layer was separated, washed with MTBE, the combined organic layer was washed with brine, dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by flash chromatography (hexane/ethyl acetate 5:1) to obtain 2-benzyl 6-*tert*-butyl 5-ethyl 2,6-diazaspiro[3.4]octane-2,5,6-tricarboxylate (**6c**) (36 g, 0.086 mol, 96%).

Step 6. Synthesis of 2-((benzyloxy)carbonyl)-6-(tert-butoxycarbonyl)-2,6-diazaspiro[3.4]octane-5-carboxylic acid (**7c**)

2-Benzyl 6-*tert*-butyl 5-ethyl 2,6-diazaspiro[3.4]octane-2,5,6-tricarboxylate (**6c**) (36 g, 0.086 mol) was dissolved in dry THF (360 mL) and solution of lithium hydroxide monohydrate (10.8 g, 0.256 mol) in water (60 mL) was added to the reaction mixture, which was stirred at room temperature overnight. The resulting mixture was poured into distilled water (400 mL), and the aqueous layer was washed with MTBE (2×200

mL). The water fraction was acidified with sodium hydrogen sulfate (36.1 g, 0.3 mol) and then extracted with ethyl acetate (2×300 mL). After that the organic fractions were combined, dried over sodium sulfate and concentrated *in vacuo* to obtain 2-[(benzyloxy)carbonyl]-6-[(tert-butoxy)carbonyl]-2,6-diazaspiro[3.4]octane-5-carboxylic acid (**7c**) (20 g, 0.051 mol, 59%).

2-((Benzyloxy)carbonyl)-6-(*tert*-butoxycarbonyl)-2,6-diazaspiro[3.4]octane-5-carboxylic acid (7c)

6 Steps yield: 20 g, 0.051 mol, 7.3%. Light-green crystalline powder. Mp: 44–47 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39 – 7.28 (m, 5H), 5.10 (s, 2H), 4.38 – 4.17 (m, 2H), 4.04 – 3.76 (m, 3H), 3.70 – 3.50 (m, 1H), 3.41 – 3.24 (m, 1H), 2.33 – 2.08 (m, 2H), 1.52 – 1.36 (m, 9H) ppm, CO_2H proton is in exchange. $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$): δ 171.05, 170.83, 154.30, 153.72, 80.07, 79.96, 66.63, 66.11, 61.01, 60.91, 59.23, 59.15, 52.20, 52.06, 48.30, 47.29, 44.51, 44.13, 34.89, 34.13, 28.36, 28.26, 14.40, 14.30 ppm. LCMS: $[M - H]^-$ 284.2. Anal. Calcd for $C_{20}H_{26}N_2O_6$, %: C 61.53, H 6.71, N 7.18. Found, %: C 61.65, H 6.77, N 7.10.

6-(*tert*-Butyl) 5-ethyl 2,6-diazaspiro[3.4]octane-5,6-dicarboxylate (15c)

2-Benzyl 6-(*tert*-butyl) 5-ethyl 2,6-diazaspiro[3.4]octane-2,5,6-tricarboxylate (**6c**) (40 g, 0.096 mol) was dissolved in dry methanol (500 mL), 10% Pd/C (1 g) was added and the flask was vacuumed while stirring using a water jet pump. After 10-15 minutes, the pump was disconnected and the flask was joined to a rubber bulb with H_2. The reaction mixture was left to hydrogenate overnight. Then the reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was dissolved in MTBE (400 mL) and washed with cold 10% aqueous potassium hydroxide solution (100 mL). The MTBE layer was dried over sodium sulfate and concentrated *in vacuo* to give 6-(*tert*-butyl) 5-ethyl 2,6-diazaspiro[3.4]octane-5,6-dicarboxylate (20 g, 0.07 mol, 73%).

Yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.32 – 4.11 (m, 3H), 3.94 – 3.52 (m, 3H), 3.48 – 3.25 (m, 3H), 2.30 – 2.06 (m, 3H), 1.49 – 1.36 (m, 9H), 1.28 (q, J = 7.6 Hz, 3H) ppm. $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$): δ 171.73, 155.98, 153.23, 135.72, 135.63, 128.01, 127.71, 127.67, 127.58, 127.54, 80.40, 66.68, 66.56, 65.44, 64.75, 43.92, 43.53, 42.89, 41.82, 34.32, 33.66, 27.84, 27.71 ppm. LCMS: $[M + H]^+$ 285.2. Anal. Calcd for $C_{14}H_{24}N_2O_4$, %: C 59.14, H 8.51, N 9.85. Found, %: C 59.29, H 8.44, N 10.01.

SYNTHETIC PROCEDURES FOR THE ROUTE B STRATEGY EMPLOYING METHYL CARBOXYLATES AS THE STARTING COMPOUNDS

2-(*tert*-Butoxycarbonyl)-2-azaspiro[4.4]nonane-1-carboxylic acid (7d)

Step 1. Synthesis of methyl 1-(cyanomethyl)cyclopentane-1-carboxylate[74] (**9d**)

Diisopropylamine (146 mL, 1.03 mol) was dissolved in dry THF (1.2 L), the solution was cooled to -78°C and butyl lithium (412 mL, 16% solution in hexane, 1.03 mol) was added in one portion. The reaction mixture was stirred for 30 minutes at -20°C. Then a solution of methyl cyclopentanecarboxylate (**8d**) (120 g, 0.94 mol) in dry THF (150 mL) was added dropwise at -78°C, and the resulting mixture was stirred

at -78°C for 1 hour. After that, a solution of bromoacetonitrile (84.8 mL, 1.22 mol) in dry THF (100 mL) was added dropwise at -78°C, and the reaction mixture was warmed to room temperature and left to stir for 16 hours. Upon completion, the reaction mass was cooled to 0°C and an aqueous solution of ammonium chloride (400 mL) was added dropwise. The reaction mixture was poured into ethyl acetate, and the organic phase was separated. The water fraction was additionally washed with ethyl acetate and the combined organic layers were dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by flash chromatography (hexane/ethyl acetate 5:1) to give methyl 1-(cyanomethyl)cyclopentanecarboxylate (**9d**) (96 g, 0.574 mol, 61%).

Step 2. Synthesis of 2-azaspiro[4.4]nonan-1-one[74] (**10d**)

Freshly prepared Raney nickel (40 g) was placed in an autoclave, then a solution of methyl 1-(cyanomethyl)cyclopentanecarboxylate (**9d**) (96 g, 0.574 mol) in methanol/ammonia (1.8 L) was added and the reaction mixture was stirred in the autoclave at room temperature for two days under H_2 pressure of 50 atm. After that, the reaction mixture was filtered, the filtrate was concentrated under reduced pressure to obtain 2-azaspiro[4.4]nonan-1-one (**10d**) (69.6 g, 0.5 mol, 87%).

White crystalline powder. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.34 (s, 1H), 3.29 (t, J = 6.7 Hz, 2H), 2.03 – 1.89 (m, 4H), 1.85 – 1.72 (m, 2H), 1.71 – 1.59 (m, 2H), 1.59 – 1.50 (m, 2H) ppm. GCMS: $[M]^{+\bullet}$ 139. Anal. Calcd for $C_8H_{13}NO$, %: C 69.03, H 9.41, N 10.06. Found, %: C 68.88, H 9.49, N 10.13.

Step 3. Synthesis of tert-butyl 1-oxo-2-azaspiro[4.4]nonane-2-carboxylate (**11d**)

2-Azaspiro[4.4]nonan-1-one (**10d**) (69.6 g, 0.5 mol) was dissolved in dry dichloromethane (800 mL), then triethylamine (104.5 mL, 0.75 mol) and DMAP (6.1 g, 0.05 mol) were added. After that the reaction mixture was cooled in an ice bath and Boc_2O (126.5 mL, 0.55 mol) was added dropwise. The resulting mixture was stirred at room temperature for 16 hours, then washed with a saturated solution of sodium chloride and 10% solution of sodium hydrogen sulfate (2×400 mL), dried over sodium sulfate and concentrated *in vacuo* to obtain *tert*-butyl 1-oxo-2-azaspiro[4.4] nonane-2-carboxylate (**11d**) (50 g, 0.2 mol, 40%).

Step 4. Synthesis of tert-butyl 1-hydroxy-2-azaspiro[4.4]nonane-2-carboxylate (**12d**)

tert-Butyl 1-oxo-2-azaspiro[4.4]nonane-2-carboxylate (**11d**) (50 g, 0.209 mol) was dissolved in dry THF (1 L), the solution was cooled to -78°C. Keeping the temperature lithium triethylborohydride (265.6 mL, 10% solution in THF, 0.25 mol) was slowly added, and the resulting mixture was stirred at -78°C for 30 minutes. A saturated solution of sodium carbonate (66.4 g, 0.626 mol) was added dropwise at -78°C, the internal temperature was raised to 0°C followed by dropwise adding 30% hydrogen peroxide (13.9 mL). The reaction mixture was stirred for 30 minutes and poured into ethyl acetate. The organic layer was separated, dried over sodium sulfate and concentrated under reduced pressure to obtain crude *tert*-butyl 1-hydroxy-2-azaspiro[4.4]nonane-2-carboxylate (**12d**) (54 g, 0.223 mol, 107%).

Step 5. Synthesis of tert-butyl 1-cyano-2-azaspiro[4.4]nonane-2-carboxylate (**13d**)

tert-Butyl 1-hydroxy-2-azaspiro[4.4]nonane-2-carboxylate (**12d**) (54 g, 0.223 mol) and trimethylsilyl cyanide (69.8 mL, 0.558 mol) were mixed in dry dichloromethane (1 L), the mixture was cooled to -78°C and to boron trifluoride etherate (84.5 mL, 0.67 mol) was added dropwise to the reaction mixture. The content was stirred at -78°C for 4 hours. Then keeping the same temperature a saturated solution of sodium carbonate (118 g, 1.116 mol) was added dropwise, the temperature was raised to room temperature, and the reaction mixture was poured into a mixture of dichloromethane and water. The organic layer was separated, dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate 5:1) to obtain *tert*-butyl 1-cyano -2-azaspiro[4.4]nonane-2-carboxylate (**13d**) (38 g, 0.151 mol, 68%).

Step 6. Synthesis of 2-azaspiro[4.4]nonane-1-carboxylic acid hydrochloride (**14d**)

tert-Butyl 1-cyano-2-azaspiro[4.4]nonane-2-carboxylate (**13d**) (38 g, 0.151 mol) was suspended in 35% aqueous hydrochloric acid solution (400 mL) and the reaction mixture was refluxed overnight. Upon completion, the reaction mixture was cooled, water (200 mL) was added, and the mixture was washed with MTBE (2×300 mL). The aqueous layer was separated, concentrated *in vacuo,* and the residue of 2-azaspiro[4.4]nonane-1-carboxylic acid hydrochloride (**14d**) (30 g, 0.145 mol) was used in the next step without purification.

Step 7. Synthesis of 2-(tert-butoxycarbonyl)-2-azaspiro[4.4]nonane-1-carboxylic acid (**7d**)

2-Azaspiro[4.4]nonane-1-carboxylic acid hydrochloride (**14d**) (30 g, 0.145 mol) was dissolved in the THF/water mixture (300/150 mL), then potassium carbonate (60.4 g, 0.44 mol) was added portionwise to the reaction mixture followed by Boc_2O (40.2 mL, 0.17 mol) dropwise. The reaction mass was stirred at room temperature for 16 hours. Upon completion, the resulting mixture was poured into water (300 mL), washed with MTBE (2×100 mL). The aqueous layer was separated, acidified with sodium hydrogen sulfate (61.3 g, 0.51 mol), and extracted with ethyl acetate (2×200 mL). The organic fraction was dried over sodium sulfate and concentrated *in vacuo* to furnish 2-(*tert*-butoxycarbonyl)-2-azaspiro[4.4]nonane-1-carboxylic acid (**7d**) (20 g, 0.074 mol, 50%).

2-(*tert*-Butoxycarbonyl)-2-azaspiro[4.4]nonane-1-carboxylic acid (7d)

7 Steps yield: 20 g, 0.074 mol, 7.9%. Light-beige powder. Mp: 138–141 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.50 (s, 1H), 3.76 – 3.69 (m, 1H), 3.49 – 3.39 (m, 1H), 3.31 – 3.16 (m, 1H), 1.82 (dq, J = 20.1, 9.8, 9.3 Hz, 1H), 1.71 – 1.47 (m, 8H), 1.45 – 1.23 (m, 10H) ppm. ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 179.41, 178.58, 156.02, 155.24, 81.44, 81.25, 68.81, 68.20, 54.83, 53.88, 46.53, 46.22, 39.79, 39.75, 36.75, 36.07,

34.63, 34.50, 29.57, 29.43, 25.19, 24.81 ppm. LCMS: $[M - H]^-$ 268.2. Anal. Calcd for $C_{14}H_{23}NO_4$, %: C 62.43, H 8.61, N 5.20. Found, %: C 62.54, H 8.52, N 5.32.

2-(*tert*-Butoxycarbonyl)-2-azaspiro[4.5]decane-1-carboxylic acid (7e)

Step 1. Synthesis of methyl 1-(cyanomethyl)cyclohexane-1-carboxylate (**9e**)

Diisopropylamine (155.6 mL, 1.1 mol) was dissolved in dry THF (1.5 L), the solution was cooled to -78°C and butyl lithium (440 mL, 16% solution in hexane, 1.10 mol) was added in one portion. The reaction mixture was stirred for 30 minutes at -20°C. Then a solution of methyl cyclohexanecarboxylate (**8e**) (120 g, 0.84 mol) in dry THF (100 mL) was added dropwise at -78°C, and the resulting mixture was stirred at -78°C for 1 hour. After that, a solution of bromoacetonitrile (70.5 mL, 1.00 mol) in dry THF (100 mL) was added dropwise at -78°C, and the reaction mixture was warmed to room temperature and left to stir for 16 hours. Upon completion, the reaction mass was cooled to 0°C and an aqueous solution of ammonium chloride (300 mL) was added dropwise. The reaction mixture was poured into ethyl acetate, and the organic phase was separated. The water fraction was additionally washed with ethyl acetate and the combined organic layers were dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by flash chromatography (hexane/ethyl acetate 5:1) to give methyl 1-(cyanomethyl)cyclohexanecarboxylate (**9e**) (90 g, 0.497 mol, 59%).

Step 2. Synthesis of 2-azaspiro[4.5]decan-1-one (**10e**)

Freshly prepared Raney nickel (40 g) was placed in an autoclave, then a solution of methyl 1-(cyanomethyl)cyclohexanecarboxylate (**9e**) (90 g, 0.497 mol) in methanol/ammonia (1.8 L) was added and the reaction mixture was stirred in the autoclave at room temperature for two days under H_2 pressure of 50 atm. After that, the reaction mixture was filtered, the filtrate was concentrated under reduced pressure to obtain 2-azaspiro[4.5]decane-1-one (**10e**) (65.6 g, 0.428 mol, 86%).

White crystalline powder. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.05 (s, 1H), 3.30 (t, J = 6.9 Hz, 2H), 2.03 (t, J = 6.9 Hz, 2H), 1.75 – 1.60 (m, 5H), 1.49 – 1.41 (m, 2H), 1.38 – 1.25 (m, 3H) ppm. GCMS: $[M]^{+\bullet}$ 153. Anal. Calcd for $C_9H_{15}NO$, %: C 70.55, H 9.87, N 9.14. Found, %: C 70.39, H 9.94, N 9.20.

Step 3. Synthesis of tert-butyl 1-oxo-2-azaspiro[4.5]decane-2-carboxylate (**11e**)

2-Azaspiro[4.5]decane-1-one (**10e**) (65.6 g, 0.428 mol) was dissolved in dry dichloromethane (700 mL), then triethylamine (89.5 mL, 0.64 mol) and DMAP (5.23 g, 0.043 mol) were added. After that the reaction mixture was cooled in an ice bath and Boc_2O (118.0 mL, 0.51 mol) was added dropwise. The resulting mixture was stirred at room temperature for 16 hours, then washed with a saturated solution of sodium chloride and solution of sodium hydrogen sulfate, dried over sodium sulfate and concentrated *in vacuo* to obtain *tert*-butyl 1-oxo-2-azaspiro[4.5]decane-2-carboxylate (**11e**) (71.3 g, 0.28 mol, 65%).

Step 4. Synthesis of tert-butyl 1-hydroxy-2-azaspiro[4.5]decane-2-carboxylate (**12e**)

tert-Butyl 1-oxo-2-azaspiro[4.5]decane-2-carboxylate (**11e**) (71.3 g, 0.28 mol) was dissolved in dry THF (1.4 L), the solution was cooled to -78°C. While keeping the temperature lithium triethylborohydride (238.5 mL, 15% solution in hexane, 0.338 mol) was slowly added, and the resulting mixture was stirred at -78°C for 30 minutes. A saturated solution of sodium carbonate (89.5 g, 0.844 mol) was added dropwise at -78°C, the internal temperature was raised to 0°C followed by dropwise adding 30% hydrogen peroxide (31.3 mL). The reaction mixture was stirred for 30 minutes and poured into ethyl acetate. The organic layer was separated, dried over sodium sulfate and concentrated under reduced pressure to obtain crude *tert*-butyl 1-hydroxy-2-azaspiro[4.5]decane-2-carboxylate (**12e**) (70 g, 0.274 mol, 98%).

Step 5. Synthesis of tert-butyl 1-cyano-2-azaspiro[4.5]decane-2-carboxylate (**13e**)

tert-Butyl 1-hydroxy-2-azaspiro[4.5]decane-2-carboxylate (**12e**) (70 g, 0.274 mol) and trimethylsilyl cyanide (85.7 mL, 0.685 mol) were mixed in dry dichloromethane (1.1 L), the mixture was cooled to -78°C and to boron trifluoride etherate (103.7 mL, 0.82 mol) was added dropwise to the reaction mixture. The content was stirred at -78°C for 4 hours. Then keeping the same temperature a saturated solution of sodium carbonate (87.2 g, 0.82 mol) was added dropwise, the temperature was raised to room temperature, and the reaction mixture was poured into a mixture of dichloromethane and water. The organic layer was separated, dried over sodium sulfate and concentrated under reduced pressure to afford *tert*-butyl 1-cyano-2-azaspiro[4.5]decane-2-carboxylate (**13e**) (60 g, 0.227 mol, 83%).

Step 6. Synthesis of 2-azaspiro[4.5]decane-1-carboxylic acid hydrochloride (**14e**)

tert-Butyl 1-cyano-2-azaspiro[4.5]decane-2-carboxylate (**13e**) (60 g, 0.227 mol) was suspended in 35% aqueous hydrochloric acid solution (800 mL) and the reaction mixture was refluxed for 16 hours. Upon completion, the reaction mixture was cooled, and washed with MTBE (2×300 mL). The aqueous layer was separated, concentrated *in vacuo,* and the residue of 2-azaspiro[4.5]decane-1-carboxylic acid hydrochloride (**14e**) (50 g, 0.227 mol, 100%) was used in the next step without purification.

Step 7. Synthesis of 2-(tert-butoxycarbonyl)-2-azaspiro[4.5]decane-1-carboxylic acid (**7e**)

2-Azaspiro[4.5]decane-1-carboxylic acid hydrochloride (**14e**) (50 g, 0.227 mol) was dissolved in the dioxane/water mixture (500/250 mL), then potassium carbonate (94.4 g, 0.68 mol) was added portionwise to the reaction mixture followed by Boc_2O (62.8 mL, 0.273 mol) dropwise. The reaction mass was stirred at room temperature for 16 hours. Upon completion, the resulting mixture was poured into water (400 mL), washed with MTBE (2×200 mL). The aqueous layer was separated, acidified with sodium hydrogen sulfate (95.6 g, 0.79 mol), and extracted with ethyl acetate (2×300 mL). The organic fraction was dried over sodium sulfate and concentrated *in vacuo* to

furnish 2-(*tert*-butoxycarbonyl)-2-azaspiro[4.5]decane-1-carboxylic acid (**7e**) (36 g, 0.127 mol, 56%).

2-(*tert*-Butoxycarbonyl)-2-azaspiro[4.5]decane-1-carboxylic acid (7e)

7-Steps yield: 36 g, 0.13 mol, 15.1%. Beige powder. Mp: 154−157 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.10 – 3.88 (m, 1H), 3.66 – 3.50 (m, 1H), 3.39 (dq, J = 18.7, 9.1 Hz, 1H), 1.92 – 1.76 (m, 2H), 1.69 – 1.31 (m, 19H) ppm, CO_2H proton is in exchange. $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$): δ 178.19, 177.49, 154.94, 154.22, 80.25, 79.99, 68.69, 67.87, 46.41, 45.35, 44.59, 44.34, 35.55, 35.44, 33.06, 33.00, 28.42, 28.26, 25.81, 22.92, 22.66 ppm. LCMS: $[M - H]^-$ 282.1. Anal. Calcd for $C_{15}H_{25}NO_4$, %: C 63.58, H 8.89, N 4.94. Found, %: C 63.72, H 8.93, N 4.80.

2-(*tert*-Butoxycarbonyl)-8,8-difluoro-2-azaspiro[4.5]decane-1-carboxylic acid (7f)

Step 1. Synthesis of methyl 1-(cyanomethyl)-4,4-difluorocyclohexane-1-carboxylate (**9f**)

Diisopropylamine (140 mL, 0.98 mol) was dissolved in dry THF (1.4 L), the solution was cooled to -78°C and butyl lithium (394.3 mL, 16% solution in hexane, 0.98 mol) was added in one portion. The reaction mixture was stirred for 30 minutes at -20°C. Then a solution of methyl 4,4-difluorocyclohexane-1-carboxylate (**8f**) (135 g, 0.757 mol) in dry THF (100 mL) was added dropwise at -78°C, and the resulting mixture was stirred at -78°C for 1 hour. After that, a solution of bromoacetonitrile (63.3 mL, 0.91 mol) in dry THF (100 mL) was added dropwise at -78°C, and the reaction mixture was warmed to room temperature and left to stir for 16 hours. Upon completion, the reaction mass was cooled to 0°C and an aqueous solution of ammonium chloride (300 mL) was added dropwise. The reaction mixture was poured into ethyl acetate, and the organic phase was separated. The water fraction was additionally washed with ethyl acetate and the combined organic layers were dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by flash chromatography (hexane/ethyl acetate 5:1) to give methyl 1-(cyanomethyl)-4,4-difluorocyclohexane-1-carboxylate (**9f**) (66 g, 0.304 mol, 40%).

Step 2. Synthesis of 8,8-difluoro-2-azaspiro[4.5]decan-1-one (**10f**)

Freshly prepared Raney nickel (25 g) was placed in an autoclave, then a solution of methyl 1-(cyanomethyl)-4,4-difluorocyclohexane-1-carboxylate (**9f**) (66 g, 0.304 mol) in methanol/ammonia (1.3 L) was added and the reaction mixture was stirred in the autoclave at room temperature for two days under H_2 pressure of 50 atm. After that, the reaction mixture was filtered, the filtrate was concentrated under reduced pressure to obtain 8,8-difluoro-2-azaspiro[4.5]decan-1-one (**10f**) (40 g, 0.211 mol, 69%).

White crystalline powder. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.05 (s, 1H), 3.30 (t, J = 6.9 Hz, 2H), 2.03 (t, J = 6.9 Hz, 2H), 1.75 – 1.60 (m, 5H), 1.49 – 1.41 (m, 2H), 1.38 – 1.25 (m, 3H) ppm. GCMS: $[M]^{+\bullet}$ 153. Anal. Calcd for $C_9H_{15}NO$, %: C 70.55, H 9.87, N 9.14. Found, %: C 70.39, H 9.94, N 9.20.

Step 3. Synthesis of tert-butyl 8,8-difluoro-1-oxo-2-azaspiro[4.5]decane-2-carboxylate (**11f**)

8,8-Difluoro-2-azaspiro[4.5]decan-1-one (**10f**) (40 g, 0.211 mol) was dissolved in dry dichloromethane (400 mL), then triethylamine (44.2 mL, 0.32 mol) and DMAP (2.6 g, 0.021 mol) were added. After that the reaction mixture was cooled in an ice bath and Boc_2O (58.34 mL, 0.25 mol) was added dropwise. The resulting mixture was stirred at room temperature for 16 hours, then washed with a saturated solution of sodium chloride and 10% solution of sodium hydrogen sulfate (2×300 mL), dried over sodium sulfate and concentrated *in vacuo* to obtain *tert*-butyl 8,8-difluoro-1-oxo-2-azaspiro[4.5]decane-2-carboxylate (**11f**) (55 g, 0.19 mol, 90%).

Step 4. Synthesis of tert-butyl 8,8-difluoro-1-hydroxy-2-azaspiro[4.5]decane-2-carboxylate (**12f**)

tert-Butyl 8,8-difluoro-1-oxo-2-azaspiro[4.5]decane-2-carboxylate (**11f**) (55 g, 0.19 mol) was dissolved in dry THF (1.1 L), the solution was cooled to -78°C. While keeping the temperature, lithium triethylborohydride (120.8 mL, 20% solution in THF, 0.228 mol) was slowly added, and the resulting mixture was stirred at -78°C for 30 minutes. A saturated solution of sodium carbonate (60.4 g, 0.57 mol) was added dropwise at -78°C, the internal temperature was raised to 0°C followed by dropwise adding 30% hydrogen peroxide (21.1 mL). The reaction mixture was stirred for additional 30 minutes and poured into ethyl acetate. The organic layer was separated, dried over sodium sulfate and concentrated under reduced pressure to obtain crude *tert*-butyl 8,8-difluoro-1-hydroxy-2-azaspiro[4.5]decane-2-carboxylate (**12f**) (53 g, 0.182 mol, 96%).

Step 5. Synthesis of tert-butyl 1-cyano-8,8-difluoro-2-azaspiro[4.5]decane-2-carboxylate (**13f**)

tert-Butyl 8,8-difluoro-1-hydroxy-2-azaspiro[4.5]decane-2-carboxylate (**12f**) (53 g, 0.182 mol) and trimethylsilyl cyanide (56.9 mL, 0.45 mol) were mixed in dry dichloromethane (0.8 L), the mixture was cooled to -78°C and to boron trifluoride etherate (68.85 mL, 0.54 mol) was added dropwise to the reaction mixture. The content was stirred at -78°C for 4 hours. Then while keeping the same temperature a saturated solution of sodium carbonate (96.4 g, 0.91 mol) was added dropwise, the temperature was raised to room temperature, and the reaction mixture was poured into a mixture of dichloromethane and water. The organic layer was separated, dried over sodium sulfate and concentrated under reduced pressure to afford crude *tert*-butyl 1-cyano-8,8-difluoro-2-azaspiro[4.5]decane-2-carboxylate (**13f**) (46 g).

Step 6. Synthesis of 8,8-difluoro-2-azaspiro[4.5]decane-1-carboxylic acid hydrochloride (**14f**)

tert-Butyl 1-cyano-8,8-difluoro-2-azaspiro[4.5]decane-2-carboxylate (**13f**) from the previous step (46 g) was suspended in acetic acid (30.6 mL, 0.536 mol) followed by slow addition of 35% aqueous hydrochloric acid solution (320 mL, 3.06 mol) and the reaction mixture was heated overnight at 95°C. Upon completion, the reaction

mixture was cooled, a precipitate formed was filtered off giving crude 8,8-difluoro-2-azaspiro[4.5]decane-1-carboxylic acid hydrochloride (**14f**) (24 g, 0.094 mol) that was used in the next step without purification.

Step 7. Synthesis of 2-(tert-butoxycarbonyl)-8,8-difluoro-2-azaspiro[4.5]decane-1-carboxylic acid (**7f**)

8,8-Difluoro-2-azaspiro[4.5]decane-1-carboxylic acid hydrochloride (**14f**) (24 g, 0.094 mol) was dissolved in a dioxane/water mixture (240/120 mL), then potassium carbonate (39 g, 0.281 mol) was added portionwise to the reaction mixture followed by Boc_2O (26.6 mL, 0.122 mol) dropwise. The reaction mass was stirred at room temperature for 16 hours. Upon completion, the resulting mixture was poured into water (300 mL), washed with MTBE (2×200 mL). The aqueous layer was separated, acidified with sodium hydrogen sulfate (39.4 g, 0.33 mol), and extracted with ethyl acetate (2×200 mL). The organic fraction was dried over sodium sulfate and concentrated *in vacuo* to furnish 2-(*tert*-butoxycarbonyl)-8,8-difluoro-2-azaspiro[4.5]decane-1-carboxylic acid (**7f**) (20 g, 0.063 mol, 67%).

2-(*tert*-Butoxycarbonyl)-8,8-difluoro-2-azaspiro[4.5]decane-1-carboxylic acid (7f)

7-Steps yield: 20 g, 0.06 mol, 8.3%. White powder. Mp: 164−167 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.19 – 3.97 (m, 1H), 3.74 – 3.56 (m, 1H), 3.42 (dt, J = 18.7, 9.1 Hz, 1H), 2.21 – 1.56 (m, 10H), 1.51 – 1.35 (m, 9H) ppm, CO_2H proton is in exchange. $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 177.36, 176.58, 154.96, 154.04, 80.74, 80.58, 66.87, 65.92, 44.97, 44.35, 44.15, 43.93, 33.94, 32.79, 31.43, 30.88, 30.49, 29.31, 28.38, 28.24 ppm. 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 56.31, H 7.33, N 4.29.

2-(*tert*-Butoxycarbonyl)-8-oxa-2-azaspiro[4.5]decane-1-carboxylic acid (7g)

Step 1. Synthesis of methyl 4-(cyanomethyl)tetrahydro-2H-pyran-4-carboxylate (**9g**)

Diisopropylamine (153 mL, 1.08 mol) was dissolved in dry THF (1.5 L), the solution was cooled to -78°C and butyl lithium (433 mL, 16% solution in hexane, 1.08 mol) was added in one portion. The reaction mixture was stirred for 30 minutes at -20°C. Then a solution of methyl tetrahydro-2*H*-pyran-4-carboxylate (**8g**) (120 g, 0.83 mol) in dry THF (100 mL) was added dropwise at -78°C, and the resulting mixture was stirred at -78°C for 1 hour. After that, a solution of bromoacetonitrile (70.5 mL, 1.00 mol) in dry THF (100 mL) was added dropwise at -78°C, and the reaction mixture was warmed to room temperature and left to stir for 16 hours. Upon completion, the reaction mass was cooled to 0°C and an aqueous solution of ammonium chloride (300 mL) was added dropwise. The reaction mixture was poured into ethyl acetate, and the organic phase was separated. The water fraction was additionally washed with ethyl acetate and the combined organic layers were dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by flash chromatography

(hexane/ethyl acetate 5:1) to give methyl 4-(cyanomethyl)tetrahydro-2H-pyran-4-carboxylate (**9g**) (66 g, 0.36 mol, 43%).

Step 2. Synthesis of 8-oxa-2-azaspiro[4.5]decan-1-one (**10g**)

Freshly prepared Raney nickel (25 g) was placed in an autoclave, then a solution of methyl 4-(cyanomethyl)tetrahydro-2*H*-pyran-4-carboxylate (**9g**) (66 g, 0.36 mol) in methanol/ammonia (1.3 L) was added and the reaction mixture was stirred in the autoclave at room temperature for two days under H_2 pressure of 50 atm. After that, the reaction mixture was filtered, the filtrate was concentrated under reduced pressure to obtain 8-oxa-2-azaspiro[4.5]decan-1-one (**10g**) (48 g, 0.31 mol, 86%).

Step 3. Synthesis of tert-butyl 1-oxo-8-oxa-2-azaspiro[4.5]decane-2-carboxylate (**11g**)

8-Oxa-2-azaspiro[4.5]decan-1-one (**10g**) (48 g, 0.31 mol) was dissolved in dry dichloromethane (500 mL), then triethylamine (64.6 mL, 0.46 mol) and DMAP (3.78 g, 0.03 mol) were added. After that the reaction mixture was cooled in an ice bath and Boc_2O (78.0 mL, 0.34 mol) was added dropwise. The resulting mixture was stirred at room temperature for 16 hours, then washed with a saturated solution of sodium chloride and 10% solution of sodium hydrogen sulfate (2×300 mL), dried over sodium sulfate and concentrated *in vacuo* to obtain *tert*-butyl 1-oxo-8-oxa-2-azaspiro[4.5]decane-2-carboxylate (**11g**) (74 g, 0.29 mol, 94%).

Step 4. Synthesis of tert-butyl 1-hydroxy-8-oxa-2-azaspiro[4.5]decane-2-carboxylate (**12g**)

tert-Butyl 1-oxo-8-oxa-2-azaspiro[4.5]decane-2-carboxylate (**11g**) (74 g, 0.29 mol) was dissolved in dry THF (1.5 L), the solution was cooled to -78°C. While keeping the temperature, lithium triethylborohydride (368 mL, 10% solution in THF, 0.35 mol) was slowly added, and the resulting mixture was stirred at -78°C for 30 minutes. A saturated solution of sodium carbonate (92.1 g, 0.87 mol) was added dropwise at -78°C, the internal temperature was raised to 0°C followed by dropwise adding 30% hydrogen peroxide (32.2 mL). The reaction mixture was stirred for 30 minutes and poured into ethyl acetate. The organic layer was separated, dried over sodium sulfate and concentrated under reduced pressure to obtain crude *tert*-butyl 1-hydroxy-8-oxa-2-azaspiro[4.5]decane-2-carboxylate (**12g**) (80 g, 0.31 mol, 107%).

Step 5. Synthesis of tert-butyl 1-cyano-8-oxa-2-azaspiro[4.5]decane-2-carboxylate (**13g**)

tert-Butyl 1-hydroxy-8-oxa-2-azaspiro[4.5]decane-2-carboxylate (**12g**) (80 g, 0.31 mol) and trimethylsilyl cyanide (97.2 mL, 0.777 mol) were mixed in dry dichloromethane (1.3 L), the mixture was cooled to -78°C and to boron trifluoride etherate (117.6 mL, 0.93 mol) was added dropwise to the reaction mixture. The content was stirred at -78°C for 4 hours. Then keeping the same temperature a saturated solution of sodium carbonate (131.8 g, 1.24 mol) was added dropwise, the temperature was raised to room temperature, and the reaction mixture was poured into a mixture of dichloromethane and water. The organic layer was separated, dried

over sodium sulfate and concentrated under reduced pressure to afford crude *tert*-butyl 1-cyano-8-oxa-2-azaspiro[4.5]decane-2-carboxylate (**13g**) (71 g).

Step 6. Synthesis of 8-oxa-2-azaspiro[4.5]decane-1-carboxylic acid hydrochloride (**14g**)

tert-Butyl 1-cyano-8-oxa-2-azaspiro[4.5]decane-2-carboxylate (**13g**) (71 g) was suspended in 35% aqueous hydrochloric acid solution (1.2 L) and the reaction mixture was refluxed for 16 hours. Upon completion, the reaction mixture was cooled, and washed with MTBE (2×300 mL). The aqueous layer was separated, concentrated *in vacuo,* and the residue of 8-oxa-2-azaspiro[4.5]decane-1-carboxylic acid hydrochloride (**14g**) (59 g, 0.266 mol) was used in the next step without purification.

Step 7. Synthesis of 2-(tert-butoxycarbonyl)-8-oxa-2-azaspiro[4.5]decane-1-carboxylic acid (**7g**)

8-Oxa-2-azaspiro[4.5]decane-1-carboxylic acid hydrochloride (**14g**) (59 g, 0.266 mol) was dissolved in the dioxane/water mixture (590/295 mL), then potassium carbonate (92 g, 0.665 mol) was added portionwise to the reaction mixture followed by Boc_2O (73.45 mL, 0.32 mol) dropwise. The reaction mass was stirred at room temperature for 16 hours. Upon completion, the resulting mixture was poured into water (500 mL), washed with MTBE (2×200 mL). The aqueous layer was separated, acidified with sodium hydrogen sulfate (95.8 g, 0.80 mol), and extracted with ethyl acetate (2×300 mL). The organic fraction was dried over sodium sulfate and concentrated *in vacuo* to furnish 2-(*tert*-butoxycarbonyl)-2-azaspiro[4.5]decane-1-carboxylic acid (**7g**) (28 g, 0.10 mol, 38%).

2-(*tert*-Butoxycarbonyl)-8-oxa-2-azaspiro[4.5]decane-1-carboxylic acid (7g)

7-Steps yield: 28 g, 0.10 mol, 12.1%. Beige powder. Mp: 123–125 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.25 – 4.00 (m, 1H), 3.87 – 3.56 (m, 5H), 3.41 (dq, J = 19.3, 10.0, 9.3 Hz, 1H), 2.02 – 1.84 (m, 2H), 1.80 – 1.65 (m, 2H), 1.61 – 1.38 (m, 11H) ppm, CO_2H proton is in exchange. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 176.23, 175.55, 154.45, 153.62, 80.08, 79.90, 67.23, 66.16, 64.38, 64.27, 63.96, 43.68, 43.51, 43.42, 42.40, 35.02, 34.98, 32.50, 32.42, 27.89, 27.76 ppm. 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 8.04, N 5.02.

1-(*tert*-Butoxycarbonyl)-3,3-dimethylpyrrolidine-2-carboxylic acid (7h)

Step 1. Synthesis of methyl 3-cyano-2,2-dimethylpropanoate[74] (**9h**)

Diisopropylamine (266 mL, 1.88 mol) was dissolved in dry THF (2.7 L), the solution was cooled to -70°C and butyl lithium (755 mL, 16% solution in hexane, 1.88 mol) was added dropwise. The reaction mixture was stirred for 30 minutes at -70°C. Then a solution of methyl isobutyrate (**8h**) (175 g, 1.71 mol) in dry THF (200 mL) was added dropwise at -78°C, and the resulting mixture was stirred at -78°C for 45 minutes. After that, a solution of bromoacetonitrile (143.2 mL, 2.05 mol) in dry THF (200 mL) was added dropwise at -78°C, and the reaction mixture was stirred for 2 hours at -78°C, warmed to room temperature and left to stir overnight. Upon completion, the reaction mass was cooled to 0°C and an aqueous solution of

ammonium chloride (300 mL) was added dropwise. The reaction mixture was stirred for 15 minutes, the THF layer was separated and the water phase was twice extracted with ethyl acetate. Combined organic layers were dried over sodium sulfate and concentrated *in vacuo*. The residue was dispersed in a water/CH_2Cl_2 mixture, organic phase was separated, dried over sodium sulfate and concentrated *in vacuo* giving methyl 3-cyano-2,2-dimethylpropanoate (**9h**) (155 g, 1.1 mol, 64%).

Colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.74 (s, 3H), 2.60 (s, 2H), 1.37 (s, 6H) ppm. GCMS: $[M]^{+\bullet}$ 141, $[M\text{-}CO_2Me]^+$ 82 (100%). Anal. Calcd for $C_7H_{11}NO_2$, %: C 59.56, H 7.85, N 9.92. Found, %: C 59.43, H 7.91, N 9.81.

Step 2. Synthesis of 3,3-dimethylpyrrolidin-2-one[74] (**10h**)

Freshly prepared Raney nickel (65 g) was placed in an autoclave, then a solution of methyl 3-cyano-2,2-dimethylpropanoate (**9h**) (155 g, 1.1 mol) in methanol/ammonia (3.1 L) was added and the reaction mixture was stirred in the autoclave at room temperature for two days under H_2 pressure of 50 atm. After that, the reaction mixture was filtered, the filtrate was concentrated under reduced pressure to obtain 3,3-dimethylpyrrolidin-2-one (**10h**) (113 g, 1.0 mol, 91%).

Step 3. Synthesis of tert-Butyl 3,3-dimethyl-2-oxopyrrolidine-1-carboxylate[75] (**11h**)

3,3-Dimethylpyrrolidin-2-one (**10h**) (113 g, 1.0 mol) was dissolved in dry dichloromethane (1.7 L), then triethylamine (281 mL, 2.01 mol) and DMAP (6.15 g, 0.05 mol) were added. After that the reaction mixture was cooled in an ice bath and Boc_2O (254.3 mL, 1.11 mol) was added dropwise. The resulting mixture was stirred at room temperature for 16 hours, then washed with a saturated solution of sodium chloride and 10% solution of sodium hydrogen sulfate (2×850 mL), dried over sodium sulfate and concentrated *in vacuo* to obtain *tert*-butyl 3,3-dimethyl-2-oxopyrrolidine-1-carboxylate (**11h**) (185 g, 0.87 mol, 87%).

Step 4. Synthesis of tert-butyl 2-hydroxy-3,3-dimethylpyrrolidine-1-carboxylate (**12h**)

tert-Butyl 3,3-dimethyl-2-oxopyrrolidine-1-carboxylate (**11h**) (185 g, 0.87 mol) was dissolved in dry THF (600 mL), the solution was cooled to -78°C under argon atmosphere. While keeping the temperature, lithium triethylborohydride (1.0 L, 10% solution in THF, 0.98 mol) was slowly added, and the resulting mixture was stirred at -78°C for 30 minutes. A saturated solution of sodium hydrogen carbonate (1700 mL) was carefully added dropwise at -78°C, the internal temperature was raised to 0°C followed by dropwise adding 30% hydrogen peroxide (87 mL) keeping the temperature around 0°C. The reaction mixture was allowed to attain to room temperature, stirred for 30 minutes and poured into ethyl acetate. The organic layer was separated and the water fraction was washed with ethyl acetate. The combined ethyl acetate fraction was washed with brine, dried over sodium sulfate and concentrated under reduced pressure to obtain *tert*-butyl 2-hydroxy-3,3-dimethylpyrrolidine-1-carboxylate (**12h**) (161 g, 0.75 mol, 86%).

Step 5. Synthesis of tert-butyl 2-cyano-3,3-dimethylpyrrolidine-1-carboxylate (**13h**)

tert-Butyl 2-hydroxy-3,3-dimethylpyrrolidine-1-carboxylate (**12h**) (161 g, 0.75 mol) and trimethylsilyl cyanide (181.5 mL, 1.45 mol) were mixed in dry dichloromethane (2.5 L), the mixture was cooled to -78°C and to boron trifluoride etherate (218.3 mL, 1.73 mol) was added dropwise to the reaction mixture. The content was stirred at -78°C for 4 hours. Then keeping the same temperature a saturated solution of sodium carbonate (244.5 g, 2.30 mol) was added dropwise, the temperature was raised to room temperature, and the reaction mixture was poured into a mixture of dichloromethane and water. The organic layer was separated, dried over sodium sulfate and concentrated under reduced pressure to afford *tert*-butyl 2-cyano-3,3-dimethylpyrrolidine-1-carboxylate (**13h**) (137 g, 0.61 mol, 81%).

Step 6. Synthesis of 3,3-dimethylpyrrolidine-2-carboxylic acid hydrochloride (**14h**)

tert-Butyl 2-cyano-3,3-dimethylpyrrolidine-1-carboxylate (**13h**) (137 g, 0.61 mol) was suspended in 35% aqueous hydrochloric acid solution (2.1 L) and the reaction mixture was refluxed for 16 hours. Upon completion, the reaction mixture was cooled, and washed with MTBE (2×450 mL). The aqueous layer was separated, concentrated *in vacuo,* and the residue of 3,3-dimethylpyrrolidine-2-carboxylic acid hydrochloride (**14h**) (97 g, 0.54 mol, 89%) was used in the next step without purification.

Step 7. Synthesis 1-(tert-butoxycarbonyl)-3,3-dimethylpyrrolidine-2-carboxylic acid (**7h**)

3,3-Dimethylpyrrolidine-2-carboxylic acid hydrochloride (**14h**) (97 g, 0.54 mol) was dissolved in the dioxane/water mixture (1200/600 mL), then potassium carbonate (186 g, 1.35 mol) was added portionwise to the reaction mixture followed by Boc_2O (151.50 mL, 0.66 mol) dropwise. The reaction mass was stirred at room temperature for 16 hours. Upon completion, the resulting mixture was poured into water (1.2 L), washed with MTBE (2×450 mL). The aqueous layer was separated, acidified with sodium hydrogen sulfate (180 g, 1.50 mol), and extracted with ethyl acetate (2×750 mL). The organic fraction was dried over sodium sulfate and concentrated *in vacuo* to furnish 1-(*tert*-butoxycarbonyl)-3,3-dimethylpyrrolidine-2-carboxylic acid (**7g**) (95 g, 0.39 mol, 72%).

1-(*tert*-Butoxycarbonyl)-3,3-dimethylpyrrolidine-2-carboxylic acid (7h)

7-Steps yield: 95 g, 0.39 mol, 22.8%. White powder. Mp: 101−103 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.14 (s, 1H), 3.96 – 3.81 (m, 1H), 3.68 – 3.54 (m, 1H), 3.53 – 3.37 (m, 1H), 1.96 – 1.80 (m, 1H), 1.68 – 1.58 (m, 1H), 1.49 – 1.37 (m, 9H), 1.18 (s, 3H), 1.10 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 178.02, 177.24, 154.87, 154.18, 80.34, 80.10, 69.14, 68.59, 45.22, 44.90, 42.40, 41.37, 38.09, 37.47, 28.41, 28.25, 27.87, 23.66 ppm. 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 59.11, H 8.81, N 5.73.

Preparative procedure for the synthesis of 3-spiro proline hydrochlorides 14a,b,d-h

Corresponding *N*-Boc protected carboxylic acid **7** was dissolved in a small amount of dioxane and then 3-fold excess of 4M HCl solution in dioxane was added. The mixture was allowed to stir overnight at room temperature. After MTBE was added and the mixture was additionally stirred for 10 min. The formed precipitate was filtered off, washed with MTBE providing the title salts.

Synthesis of 3-spiro pyroglutamic acids 16b,c

Starting ester **4** (1.0 equiv) was placed in a flask containing 1:1 (*v*/*v*) ethanol/water mixture (5 mL per 1 mmol of **4**). Then potassium carbonate (2.0 equiv) was added and the mixture was refluxed for 3 hours. After, it was cooled to room temperature and acidified with 35% HCl to pH 1. A precipitate formed was filtered off, washed with water and dried in air affording the title acids.

References

1 Dias, D. A.; Urban, S.; Roessner, U. A historical overview of natural products in drug discovery. *Metabolites* **2012,** *2* (2), 303-36. 10.3390/metabo2020303

2 Mishra B.B., Tiwari V.K. Natural products: An evolving role in future drug discovery. *Eur. J. Med. Chem.* 2011;**46**:4769–4807. doi: 10.1016/j.ejmech.2011.07.057.

3 Rey-Ladino J., Ross A.G., Cripps A.W., McManus D.P., Quinn R. Natural products and the search for novel vaccine adjuvants. *Vaccine.* 2011;**29**:6464–6471.

4 Cragg G.M., Newman D.J. Biodiversity: A continuing source of novel drug leads. *Pure Appl. Chem.* 2005;**77**:7–24.

5 Haefner B. Drugs from the deep: Marine natural products as drug candidates. *Drug Discov. Today.* 2003;**8**:536–544. doi: 10.1016/S1359-6446(03)02713-2.

6 Butler M.S. The role of natural product in chemistry in drug discovery. *J. Nat. Prod.* 2004;**67**:2141–2153. doi: 10.1021/np040106y.

7 Newman, D. J.; Cragg, G. M. Natural Products As Sources of New Drugs over the 30 Years from 1981 to 2010. *J. Nat. Prod.* **2012,** *75* (3), 311-335. 10.1021/np200906s

8 Stratton, C. F.; Newman, D. J.; Tan, D. S. Cheminformatic comparison of approved drugs from natural product versus synthetic origins. *Bioorg Med Chem Lett* **2015,** *25* (21), 4802-4807. 10.1016/j.bmcl.2015.07.014

9 Ortholand, J. Y.; Ganesan, A. Natural products and combinatorial chemistry: back to the future. *Curr Opin Chem Biol* **2004,** *8* (3), 271-80. 10.1016/j.cbpa.2004.04.011

10 Ribaudo, G. Natural Products Chemistry: Advances in Synthetic, Analytical and Bioactivity Studies. *Molecules* **2023**, *28*, 5577. https://doi.org/10.3390/molecules28145577

11 Wu, G. (2009). Amino acids: metabolism, functions, and nutrition. *Amino Acids* 37, 1–17. doi: 10.1007/s00726-009-0269-0

12 Bröer, S. Amino Acid Transporters as Disease Modifiers and Drug Targets. *SLAS Discovery* **2018,** *23* (4), 303-320. 10.1177/2472555218755629

13 Carubelli, V., Castrini, A. I., Lazzarini, V., Gheorghiade, M., Metra, M., and Lombardi, C. (2015). Amino acids and derivatives, new treatment of chronicheart failure? *Heart Fail Rev.* 20, 39–51. doi: 10.1007/s10741-014-9436-9

14 Nitz, K., Lacy, M., and Atzler, D. (2019). Amino acids and their metabolism in atherosclerosis. *Arterioscler. Thromb. Vasc. Bio.* 39, 319–330. doi: 10.1161/ATVBAHA.118.311572

15 Barnham, K. J., Djuran, M. I., Murdoch, P. S., Ranford, J. D., and Sadler, P. J. (1996). Ring-opened adducts of the anticancer drug carboplatin with sulfur amino acids. *Inorg. Chem.* 35, 1065–1072. doi: 10.1021/ic950973d
16 Chen, A., Weber, I. T., Harrison, R. W., and Leis, J. (2006). Identification of amino acids in HIV-1 and avian sarcoma virus integrase subsites required for specific recognition of the long terminal repeat Ends. *J. Biol. Chem.* 281, 4173–4182. doi: 10.1074/jbc.M510628200
17 You, L., Zhao, M., Regenstein, J. M., and Ren, J. (2011). *In vitro* antioxidant activity and *in vivo* anti-fatigue effect of loach (Misgurnus anguillicaudatus) peptides prepared by papain digestion. *Food Chem.* 124, 188–194. doi: 10.1016/j.foodchem.2010.06.007
18 Kawaguchi, T., Izumi, N., Charlton, M. R., and Sata, M. (2011). Branched-chain amino acids as pharmacological nutrients in chronic liver disease. *Hepatology* 54, 1063–1070. doi: 10.1002/hep.24412
19 Xu, Q.; Deng, H.; Li, X.; Quan, Z.-S. Application of Amino Acids in the Structural Modification of Natural Products: A Review. *Frontiers in Chemistry* **2021,** *9*. 10.3389/fchem.2021.650569
20 Ma, C. M., Nakamura, N., Hattori, M., Kakuda, H., Qiao, J. C., and Yu, H. L. (2000). Inhibitory effects on HIV-1 protease of constituents from the wood of Xanthoceras sorbifolia. *J. Nat. Prod*. 63, 238–242. doi: 10.1021/np9902441
21 Brady, S. F., Pawluczyk, J. M., Lumma, P. K., Feng, D. M., Wai, J. M., Jones, R., et al. (2002). Design and synthesis of a pro-drug of vinblastine targeted at treatment of prostate cancer with enhanced efficacy and reduced systemic toxicity. *J. Med. Chem.* 45, 4706–4715. doi: 10.1021/jm020139f
22 Ma, C. M., Kully, M., Khan, J. K., Hattori, M., and Daneshtalab, M. (2007). Synthesis of chlorogenic acid derivatives with promising antifungal activity. *Bioorg. Med. Chem*. 15, 6830–6833. doi: 10.1016/j.bmc.2007.07.038
23 Zhang, Y. N., Zhang, W., Hong, D., Shi, L., Shen, Q., Li, J. Y., et al. (2008). Oleanolic acid and its derivatives: new inhibitor of protein tyrosine phosphatase 1B with cellular activities. *Bioorg. Med. Chem.* 16, 8697–8705. doi: 10.1016/j.bmc.2008.07.080
24 Drag-Zalesinska, M., Kulbacka, J., Saczko, J., Wysocka, T., Zabel, M., Surowiak, P., et al. (2009). Esters of betulin and betulinic acid with amino acids have improved water solubility and are selectively cytotoxic toward cancer cells. *Bioorg. Med. Chem. Lett*. 19, 4814–4817. doi: 10.1016/j.bmcl.2009.06.046
25 Kim, M. K., Park, K. S., Yeo, W. S., Choo, H., and Chong, Y. (2009). *In vitro* solubility, stability and permeability of novel quercetin-amino acid conjugates. *Bioorg. Med. Chem*. 17, 1164–1171. doi: 10.1016/j.bmc.2008.12.043
26 Anbharasi, V., Cao, N., and Feng, S. S. (2010). Doxorubicin conjugated to D-alpha-tocopheryl polyethylene glycol succinate and folic acid as a prodrug for targeted chemotherapy. *J. Biomed. Mater Res. A* 94, 730–743. doi: 10.1002/jbm.a.32734
27 Cooper, T. W. J.; Campbell, I. B.; Macdonald, S. J. F. Factors determining the selection of organic reaction by medicinal chemists and the use of these reactions in arrays (small focused libraries). Angew. Chem. Int. Ed. 2010, 49, 8082−8091.
28 Roughley, S. D.; Jordan, A. M. The medicinal chemist's toolbox: An analysis of reactions used in the pursuit of drug candidates. J. Med. Chem. 2011, 54, 3451−3479.
29 Hunt, S. The Non-Protein Amino Acids. In *Chemistry and Biochemistry of the Amino Acids*, Barrett, G. C., Ed. Springer Netherlands: Dordrecht, 1985; pp 55-138. 10.1007/978-94-009-4832-7_4
30 Xue, Y.-P.; Cao, C.-H.; Zheng, Y.-G. Enzymatic asymmetric synthesis of chiral amino acids. *Chem. Soc. Rev.* **2018,** *47* (4), 1516-1561. 10.1039/C7CS00253J
31 Narancic, T.; Almahboub, S. A.; O'Connor, K. E. Unnatural amino acids: production and biotechnological potential. *World J. Microbiol. Biotechnol.* **2019,** *35* (4), 67. 10.1007/s11274-019-2642-9
32 Blaskovich, M. A. T. Unusual Amino Acids in Medicinal Chemistry. *J. Med. Chem.* **2016,** *59* (24), 10807-10836. 10.1021/acs.jmedchem.6b00319
33 Che, Y.; Marshall, G. R. *Biopolymers* **2006**, *81*, 392.

34 Lee, C. C., Huang, K. F., Chang, D. M., Hsu, J. J., Huang, F. C., Shih, K. N., et al. (2012). Design, synthesis and evaluation of telomerase inhibitory, hTERT repressing, and anti-proliferation activities of symmetrical 1,8-disubstituted amidoanthraquinones. *Eur. J. Med. Chem*. 50, 102–112. doi: 10.1016/j.ejmech.2012.01.044
35 Jing, Y., Wang, G., Ge, Y., Xu, M., and Gong, Z. (2015). Synthesis, anti-tumor and anti-angiogenic activity evaluations of asiatic Acid amino Acid derivatives. *Molecules* 20, 7309–7324. doi: 10.3390/molecules20047309
36 Hu, X., Gao, C., Tan, C., Zhang, C., Zhang, H., Li, S., et al. (2011). Design and synthesis of N-phosphoryl peptide modified podophyllotoxin derivatives as potent anticancer agents. *Protein Pept. Lett*. 18, 1258–1264. doi: 10.2174/092986611797642652
37 (a) Zhang, K.; Schweizer, F. *Synlett* **2005**, 3111. and references cited therein. (b) Che, Y.; Marshall, G. R. *J. Org. Chem.* **2004**, *69*, 9030. (c) Quancard, J.; Labonne, A.; Jacquot, Y.; Lavielle, S.; Karoyan, P. *J. Org. Chem.* **2004**, *69*, 7940. (d) Cavelier, F.; Vivet, B.; Martinez, J.; Aubry, A.; Didierjean, C.; Vicherat, A.; Marraud, M. *J. Am. Chem. Soc.* **2002**, *124*, 2917.
38 Raghavan, S.; Lu, Z.; Beeson, T.; Chapman, K. T.; Schleif, W. A.; Olsen, D. B.; Stahlhut, M.; Rutkowski, C. A.; Gabryelski, L.; Emini, E.; Tata, J. R. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5432.
39 Beausoleil, E.; Sharma, R.; Michnick, S. W.; Lubell, W. D. Alkyl 3-Position Substituents Retard the Isomerization of Prolyl and Hydroxyprolyl Amides in Water. *J. Org. Chem.* **1998,** *63* (19), 6572-6578. 10.1021/jo980673o
40 Chalyk, B. A.; Butko, M. V.; Yanshyna, O. O.; Gavrilenko, K. S.; Druzhenko, T. V.; Mykhailiuk, P. K. Synthesis of Spirocyclic Pyrrolidines: Advanced Building Blocks for Drug Discovery. *Chem. Eur. J.* **2017,** *23* (66), 16782-16786. https://doi.org/10.1002/chem.201702362
41 Chalyk, B. A.; Isakov, A. A.; Butko, M. V.; Hrebeniuk, K. V.; Savych, O. V.; Kucher, O. V.; Gavrilenko, K. S.; Druzhenko, T. V.; Yarmolchuk, V. S.; Zozulya, S.; Mykhailiuk, P. K. Synthesis of 6-Azaspiro[4.3]alkanes: Innovative Scaffolds for Drug Discovery. *Eur. J. Org. Chem.* **2017,** *2017* (31), 4530-4542. https://doi.org/10.1002/ejoc.201700536
42 Melnykov, K. P.; Artemenko, A. N.; Ivanenko, B. O.; Sokolenko, Y. M.; Nosik, P. S.; Ostapchuk, E. N.; Grygorenko, O. O.; Volochnyuk, D. M.; Ryabukhin, S. V. Scalable Synthesis of Biologically Relevant Spirocyclic Pyrrolidines. *ACS Omega* **2019,** *4* (4), 7498-7515. 10.1021/acsomega.9b00896
43 https://www.reaxys.com/
44 Esch, P. M.; Hiemstra, H.; Nico Speckamp, W. Synthesis of cyclic α-amino acids through ring closure of glycine derived free radicals. *Tetrahedron Lett.* **1990,** *31* (5), 759-762. https://doi.org/10.1016/S0040-4039(00)94622-7
45 Esch, P. M.; Hiemstra, H.; de Boer, R. F.; Speckamp, W. N. Reductive cyclization of carbon-centered glycine radicals; a novel synthetic route to cyclic α-amino acids. *Tetrahedron* **1992,** *48* (22), 4659-4676. https://doi.org/10.1016/S0040-4020(01)81240-0
46 Xu, W.; Mariano, P. S. Substituent effects on amine cation radical acidity. Regiocontrol of .beta.-(aminoethyl)cyclohexenone photocyclizations. *J. Am. Chem. Soc.* **1991,** *113* (4), 1431-1432. 10.1021/ja00004a064
47 Xu, W.; Zhang, X. M.; Mariano, P. S. Single electron transfer promoted photocyclization reactions of (aminoalkyl)cyclohexenones. Mechanistic and synthetic features of processes involving the generation and reactions of amine cation and .alpha.-amino radicals. *J. Am. Chem. Soc.* **1991,** *113* (23), 8863-8878. 10.1021/ja00023a039
48 Tandon, M.; Wu, M.; Begley, T. P.; Myllyharju, J.; Pirskanen, A.; Kivirikko, K. Substrate specificity of human prolyl-4-hydroxylase. *Bioorg. Med. Chem. Lett.* **1998,** *8* (10), 1139-1144. https://doi.org/10.1016/S0960-894X(98)00183-8
49 Jones, B.; Proud, M.; Sridharan, V. Synthesis of oxetane/azetidine containing spirocycles via the 1,3-dipolar cycloaddition reaction. *Tetrahedron Lett.* **2016,** *57* (25), 2811-2813. https://doi.org/10.1016/j.tetlet.2016.05.053

50 Deng, H.; Jia, R.; Yang, W.-L.; Yu, X.; Deng, W.-P. Ligand-controlled switch in diastereoselectivities: catalytic asymmetric construction of spirocyclic pyrrolidine-azetidine/oxe(thie)tane derivatives. *Chem. Commun.* **2019,** *55* (51), 7346-7349. 10.1039/C9CC03589C
51 WO2014086806A1_2014
52 WO2021141751A1
53 Sannigrahi, M., Stereocontrolled synthesis of spirocyclics. *Tetrahedron* **1999,** *55* (30), 9007-9071. https://doi.org/10.1016/S0040-4020(99)00482-2
54 Fjelbye, K.; Marigo, M.; Clausen, R. P.; Juhl, K., Preparation of Spirocyclic β-Proline Esters: Geometrically Restricted Building Blocks for Medicinal Chemistry. *Synlett* **2017,** *28* (02), 231-234. 10.1055/s-0036-1588902
55 Grygoriv, G. V.; Lega, D. A.; Zaprutko, L.; Gzella, A. K.; Wieczorek-Dziurla, E.; Chernykh, V. P.; Shemchuk, L. A., Synthesis of novel spiro-condensed 2-amino-4H-pyrans based on 1,2-benzoxathiin-4(3H)-one 2,2-dioxide. *Chem. Heterocycl. Comp.* **2019,** *55* (3), 254-260. 10.1007/s10593-019-02450-4
56 Shemchuk, L. A.; Lega, D. A.; Redkin, R. G.; Chernykh, V. P.; Shishkin, O. V.; Shishkina, S. V., An efficient, three-component synthesis and molecular structure of derivatives of 2-amino-3-R-6-ethyl-4,6-dihydropyrano[3,2-c][2,1]benzothiazine-5,5-dioxide spirocombined with a 2-oxindole nucleus. *Tetrahedron* **2014,** *70* (44), 8348-8353. 10.1016/j.tet.2014.09.005
57 Medina, J. R.; Blackledge, C. W.; Erhard, K. F.; Axten, J. M.; Miller, W. H. Benzyl 2-Cyano-3,3-Dimethyl-1-pyrrolidinecarboxylate, a Versatile Intermediate for the Synthesis of 3,3-Dimethylproline Derivatives. *J. Org. Chem.* **2008,** *73* (10), 3946-3949. 10.1021/jo7027163
58 Dieter, R. K.; Sharma, R. R. A Facile Preparation of Enecarbamates. *J. Org. Chem.* **1996,** *61* (12), 4180-4184. 10.1021/jo960153y
59 Tayama, E.; Ishikawa, Y. Brønsted Acid-Catalyzed Aza-Ferrier Reaction of N,O-Allenyl Acetals: Synthesis of β-Amino-α-methylene Aldehydes. *J. Org. Chem.* **2020,** *85* (14), 9405-9414. 10.1021/acs.joc.0c01047
60 Mao, Z.-Y.; Nie, X.-D.; Feng, Y.-M.; Si, C.-M.; Wei, B.-G.; Lin, G.-Q. Cu(OTf)2 catalyzed Ugi-type reaction of N,O-acetals with isocyanides for the synthesis of pyrrolidinyl and piperidinyl 2-carboxamides. *Chem. Commun.* **2021,** *57* (73), 9248-9251. 10.1039/D1CC03113A
61 Peixoto, S.; Nguyen, T. M.; Crich, D.; Delpech, B.; Marazano, C. One-Pot Formation of Piperidine- and Pyrrolidine-Substituted Pyridinium Salts via Addition of 5-Alkylaminopenta-2,4-dienals to N-Acyliminium Ions: Application to the Synthesis of (±)-Nicotine and Analogs. *Org. Lett.* **2010,** *12* (21), 4760-4763. 10.1021/ol101783c
62 Sharma, R.; Lubell, W. D. Regioselective Enolization and Alkylation of 4-Oxo-N-(9-phenylfluoren-9-yl)proline: Synthesis of Enantiopure Proline–Valine and Hydroxyproline–Valine Chimeras. *J. Org. Chem.* **1996,** *61* (1), 202-209. 10.1021/jo9514984
63 Jeffrey Michael AxtenJesus R. Medina. WO2007016364A2. Peptide deformylase inhibitors. 2007-02-08
64 EP2272825B1, Protected amino hydroxy adamantane carboxylic acid and process for its preparation, Jeffrey A. RoblRichard B. SulskyDavid J. AugeriDavid R. MagninLawrence G. HamannDavid A. Betebenner, 2015-11-04.
65 Akhilesh Kumar and Anand K. Bachhawat. Pyroglutamic acid: throwing light on a lightly studied metabolite. CURRENT SCIENCE, VOL. 102, NO. 2, 288-297.
66 Yoshinari, O.; Igarashi, K. Anti-diabetic effect of pyroglutamic acid in type 2 diabetic Goto-Kakizaki rats and KK-Ay mice. *The British journal of nutrition* **2011,** *106* (7), 995-1004. 10.1017/s0007114511001279
67 Šudomová, M.; Hassan, S. T. S.; Khan, H.; Rasekhian, M.; Nabavi, S. M. A Multi-Biochemical and In Silico Study on Anti-Enzymatic Actions of Pyroglutamic Acid against PDE-5, ACE, and Urease Using Various Analytical Techniques: Unexplored Pharmacological Properties and Cytotoxicity Evaluation. *Biomolecules* **2019,** *9* (9), 392.

68 Liu, Q.; Batt, D. G.; Weigelt, C. A.; Yip, S.; Wu, D.-R.; Ruzanov, M.; Sack, J. S.; Wang, J.; Yarde, M.; Li, S.; Shuster, D. J.; Xie, J. H.; Sherry, T.; Obermeier, M. T.; Fura, A.; Stefanski, K.; Cornelius, G.; Khandelwal, P.; Tino, J. A.; Macor, J. E.; Salter-Cid, L.; Denton, R.; Zhao, Q.; Dhar, T. G. M. Novel Tricyclic Pyroglutamide Derivatives as Potent RORγt Inverse Agonists Identified using a Virtual Screening Approach. *ACS Medicinal Chemistry Letters* **2020,** *11* (12), 2510-2518. 10.1021/acsmedchemlett.0c00496
69 HISTIDYL PEPTIDE DERIVATIVES. Itsuo Uchida; Akira Saito; Akihiro Yasuda; Kunio Iwata; Hiroaki Hari; Katsuyoshi Hara; Mutsuyoshi Matsushita; Koretake Anami; Junichi Haruta; Noboru Furukawa. USOO5151497A, Sep. 29, 1992.
70 Heterocyclic spiro compounds and methods of use. WO2022083569A1, Brian Alan LanmanAbhisek BanerjeeMargaret CHU-MOYERDongcheng DaiJosephine ESHONDavid HuangMatthew R. KallerHeejun LeePatricia LopezVu Van MaFrancesco ManoniJose M. MEDINAAlexander J. PickrellJohn C. StellwagenZhen SunNuria A. TamayoWenhan ZHANGKai Zhu. 2022-04-28
71 Eshon, J.; Foarta, F.; Landis, C. R.; Schomaker, J. M. α-Tetrasubstituted Aldehydes through Electronic and Strain-Controlled Branch-Selective Stereoselective Hydroformylation. *J. Org. Chem.* **2018,** *83* (17), 10207-10220. 10.1021/acs.joc.8b01431
72 Fischer, C.; Smith, S. W.; Powell, D. A.; Fu, G. C. Umpolung of Michael Acceptors Catalyzed by N-Heterocyclic Carbenes. *J. Am. Chem. Soc.* **2006,** *128* (5), 1472-1473. 10.1021/ja058222q
73 Yang, X.; Kong, W.-Y.; Gao, J.-N.; Cheng, L.; Li, N.-N.; Li, M.; Li, H.-T.; Fan, J.; Gao, J.-M.; Ouyang, Q.; Xie, J.-B. Rhodium catalyzed C–C bond cleavage/coupling of 2-(azetidin-3-ylidene)acetates and analogs. *Chem. Commun.* **2019,** *55* (84), 12707-12710. 10.1039/C9CC06446J
74 Reddy, P. A.; Hsiang, B. C. H.; Latifi, T. N.; Hill, M. W.; Woodward, K. E.; Rothman, S. M.; Ferrendelli, J. A.; Covey, D. F. 3,3-Dialkyl- and 3-Alkyl-3-Benzyl-Substituted 2-Pyrrolidinones: A New Class of Anticonvulsant Agents. *J. Med. Chem.* **1996,** *39* (9), 1898-1906. 10.1021/jm9600196
75 Gawley, R. E.; Klein, R.; Ashweek, N. J.; Coldham, I. Structural studies of {6Li} 2-lithiopyrrolidines using NMR spectroscopy. *Tetrahedron* **2005,** *61* (13), 3271-3280. https://doi.org/10.1016/j.tet.2005.01.098