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Bicyclic Pyrrolidines for Medicinal Chemistry via [3 + 2]-Cycloaddition

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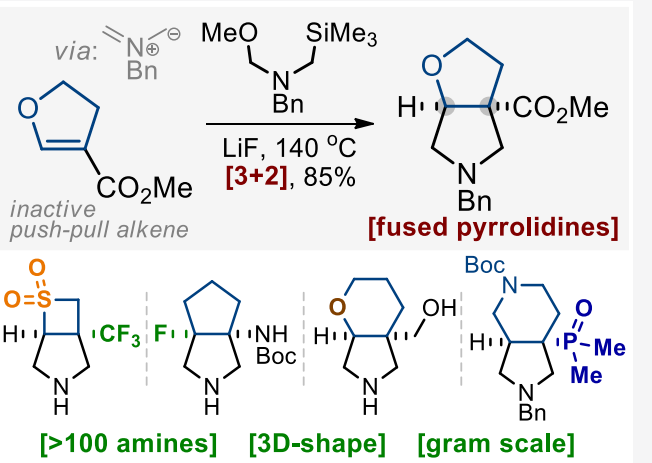
ABSTRACT: A general approach to bicyclic fused pyrrolidines via [3 + 2]-cycloaddition between nonstabilized azomethyne ylide and endocyclic electron-deficient alkenes was elaborated. "Push–pull" alkenes and CF_3-alkenes did not react with the azomethyne ylide under the previously reported conditions, and we developed a superior protocol (LiF, 140 °C, no solvent). Among obtained products were medchem-relevant bicyclic sulfones, monofluoro-, difluoro-, and trifluoromethyl-substituted pyrrolidines. This approach not only allowed preparation of novel molecules but also significantly simplified synthesis of the existing ones (e.g., sofinicline).



INTRODUCTION

Pyrrolidine is one of the most frequently used secondary amines in organic synthesis and medicinal chemistry.[1−3] The structure of more than 50 drugs comprises the fragment of pyrrolidine.[4] At the beginning of this century, a concept called "conformational restriction" appeared that changed the way medicinal chemists think.[5,6] This is because conformationally restricted compounds are often more active and selective ligands for various targets due to preorganization of a molecule in a bioactive conformation.[7] Bicyclic pyrrolidines are intrinsically conformationally restricted and, hence, of high interest to medicinal chemists (Figure 1).

Three types of bicyclic pyrrolidines exist: bridged, spirocyclic, and fused (Figure 1). In recent years, we developed practical methods to bridged,[8] spirocyclic,[9] and some fused pyrrolidines.[10] The latter class was assembled via [2 + 2]-photocycloaddition. In this work, we report a general approach to medicinal chemistry related fused pyrrolidines via [3 + 2]-cycloaddition (Figures 1 and 2).

Previously, we synthesized spirocyclic derivatives by [3 + 2]-cycloaddition between azomethyne ylide precursor **1** and exocyclic electron-deficient alkenes (Figure 2).[9] In this work, we envisioned that fused pyrrolidines could also be assembled following a similar logic starting from electron-deficient endocyclic alkenes (Figure 2). In the literature, there were indeed many examples on constructing tricyclic, polycyclic,[11] and benzoannulated compounds[12] using that approach (Figure 2). Precedents on bicyclic pyrrolidines also existed,[13] but those studies were not systematic and led to polysubstituted products with additional alkyl or aryl groups. In addition, reactions of cyclic "push–pull" alkenes and cyclic CF_3-alkenes with reagent **1** were unknown.

In this work, we developed a general approach to medchem-relevant fused bicyclic pyrrolidines via [3 + 2]-cycloaddition. Our strategy leads to derivatives with one or two functional groups and only strategic additional substituents (fluorine, *gem*-difluoro, trifluoromethyl, and sulfone) important for medicinal chemistry. To the best of our knowledge, this is the first systematic study on that topic to date.

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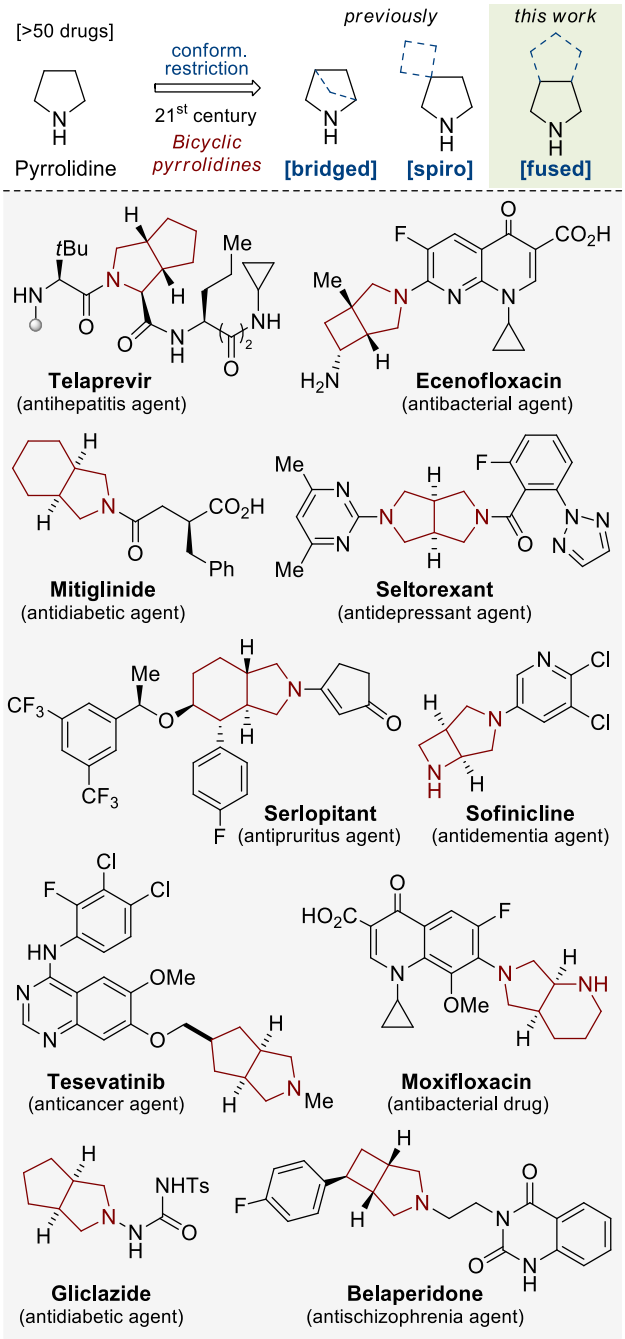

Figure 1. Bicyclic pyrrolidines in drug discovery.

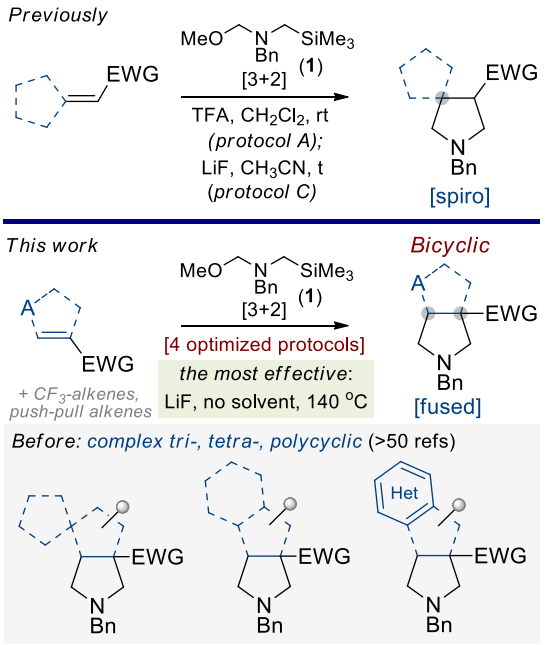

Figure 2. State of the art and objectives of this work.

RESULTS AND DISCUSSION

Optimization and Scope. Previously, during the synthesis of spirocyclic pyrrolidines,[9] we used two different conditions to generate azomethyne ylide from reagent **1**: (a) catalysis with trifluoroacetic acid (TFA) at room temperature (protocol A)[14] and catalysis with lithium fluoride (LiF) under heating in acetonitrile (protocol C).[15] For the synthesis of fused pyrrolidines, we started optimization with the same conditions. At the beginning, we easily synthesized bicyclic amines **2a**−**5a** (Scheme 1) in 87−98% yield from the corresponding active four-membered alkenes and reagent **1** using TFA catalysis at room temperature (protocol A). Products **3a**−**5a** contained the medicinal chemistry relevant sulfone moiety.[16] The structure of sulfone **3a** was proven by X-ray analysis. Under identical conditions, five-membered alkene **6** also reacted with compound **1** to provide the needed product **6a** in a lower yield of 51%. For that substrate, we somewhat optimized the conditions. We found that slow addition of compound **1** to the reaction mixture during 12 h using a syringe pump improved the yield to 77% without changing the reaction stoichiometry. In the future, we used these conditions (protocol B) for problematic substrates. Performing the reaction with LiF in acetonitrile under reflux also allowed product **6a** to be obtained in 71% yield (protocol C). Five-membered tetrasubstituted fluorine-containing alkene **7** and alkene **8** were less active than substrate **6**. However, we could obtain the needed products **7a** and **8a** in good yields by heating the reaction mixture with LiF in acetonitrile (protocol C). Unexpectedly, alkene **9** did not react under any of the previously applied conditions (Table 1). Catalysis with TFA at room temperature (protocol A) gave no product, but only the starting alkene. Slow addition of reagent **1** during 12 h (protocol B) did not give any improvement either. Performing the reaction with LiF in acetonitrile (protocol C) also did not provide any product. Presumably, the reason why alkene **9** remained inactive in [3 + 2]-cycloaddition was its "push−pull" resonance form A (Table 1). In this structure, the C(2)−C(3) bond is single and, therefore, cannot participate in the cycloaddition. Optimization of this transformation took us several years, until by accident we did not find that the reaction proceeded under heating at 140 °C without any solvent (protocol D). Luckily, the formed ylide did not polymerize at this temperature, as we originally were afraid of, but reacted with alkene **9** first. The corresponding bicyclic amine **9a** was finally isolated in 85% yield (Table 1). Moreover, the procedure was scalable, as we could synthesize ca. 20 g of the product in a single run.

Having the optimized conditions in hand—the previously known protocols A, C ande protocols B, D developed her for problematic substrates—we next studied the scope of the reaction. Five-membered oxygen-containing alkenes **10**−**13**, nitrogen-containing **14**−**17** and **19**, sulfone-containing **20**, **21**,

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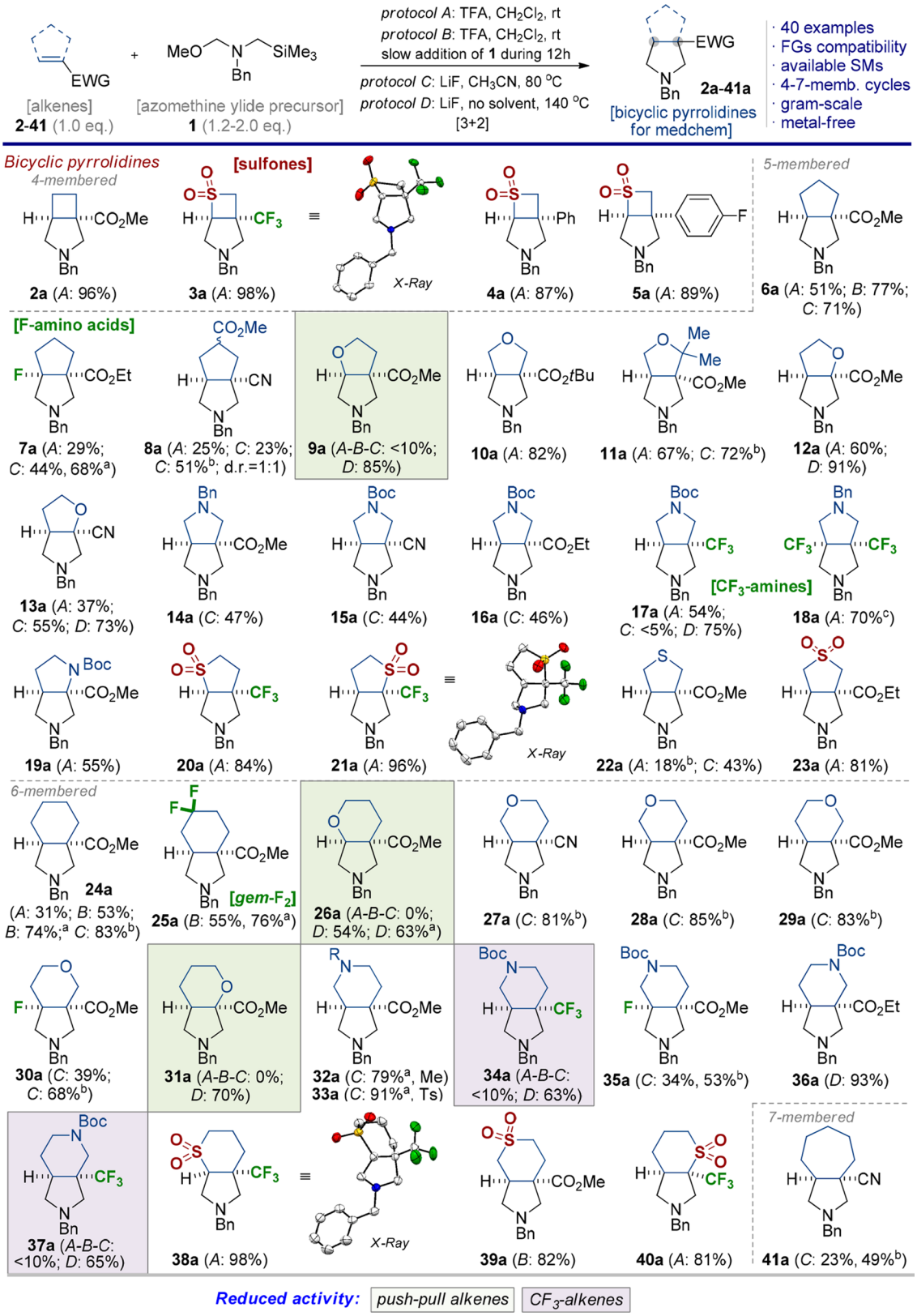
Scheme 1. Bicyclic Pyrrolidines via [3 + 2]-Cycloaddition*



*Reaction conditions: protocol A, alkene (1.0 equiv), **1** (1.2 equiv), TFA (0.1 equiv), CH_2Cl_2, 20 °C, 12 h; protocol B, alkene (1.0 equiv), slow addition of **1** (1.1 equiv) during 12 h, TFA (0.1 equiv), CH_2Cl_2, 20 °C; protocol C, alkene (1.0 equiv), **1** (1.2 equiv), LiF (3.0 equiv), CH_3CN, 80 °C, 12 h; protocol D, alkene (1.0 equiv), **1** (2.0 equiv), dry LiF (3.0 equiv), 140 °C, 12 h and 110 °C, 12 h. [a]An additional portion of **1** (0.3 equiv) was added after 12 h. [b]Two additional portions of **1** were added after 12 h (0.3 equiv) and 24 h (0.3 equiv). [c]Alkyne (CF_3−CC−CF_3, 1.0 equiv), **1** (2.0 equiv), TFA (0.2 equiv), CH_2Cl_2, −40 to +20 °C, 12 h.

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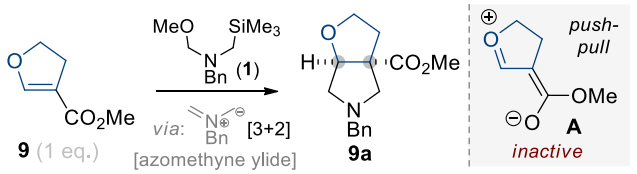
Table 1. Optimization of the [3 + 2]-Cycloaddition of Inactive Push–Pull Alkene 9 with Azomethine Ylide Precursor 1



entry	conditions	yield[a,b] (%)
	protocol A	
1	**1** (1.2 equiv), TFA (0.1 equiv), CH_2Cl_2, rt, 12 h	0
2	**1** (2 equiv)	<5
3	**1** (3 equiv)	<5
	protocol B	
4	**1** (1.2 equiv), slow addition, TFA (0.1 equiv), CH_2Cl_2, rt	<5
5	**1** (2 equiv)	<5
6	**1** (3 equiv)	<10
	protocol C	
7	**1** (1.2 equiv), LiF (3 equiv), CH_3CN, 80 °C, 12 h	0
8	**1** (2 equiv)	<5
9	**1** (3 equiv)	<10
	protocol D	
10	**1** (1.2 equiv), LiF(3eq), no solvent, 140 °C, 12 h	63
11	**1** (2 equiv), LiF (3 equiv), no solvent, 140 °C, 12 h	85[c]

[a]10 mmol. [b]Yield determined by ^1H NMR with CH_2Br_2 as an internal standard. [c]Isolated yield.

and **23**, and sulfur-containing one **22** all gave the needed bicyclic pyrrolidines **10a–23a** in good to excellent yields. Product **18a** was obtained directly from bis-trifluoromethyl acetylene (**18**) with an excess of reagent **1**. For every substrate, we initially tried the known protocols A (TFA, rt, CH_2Cl_2) and C (LiF, reflux, CH_3CN). Active alkenes, like **20** and **21**, reacted smoothly with **1** even under the conditions of protocol A. When the reaction was incomplete, we optimized it by adding more agent **1**, trying the superior protocol B (TFA, slow addition of **1**) or using the most effective protocol D (LiF, 140 °C, 12 h). The latter worked effectively on a gram scale, but on a smaller scale it was technically somewhat challenging (reaction without a solvent). Therefore, we always used this protocol last when other conditions did not work.

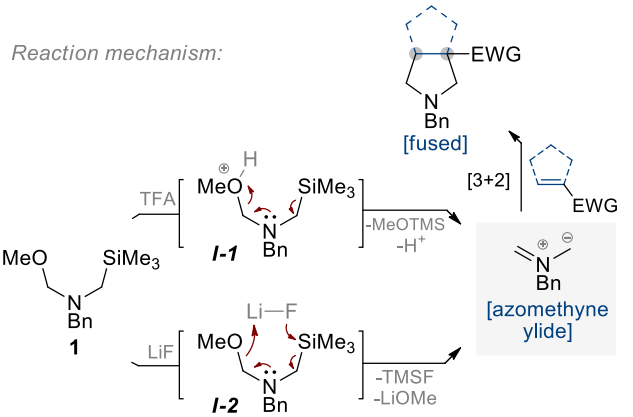
Six-membered alkene **24** was less active than the corresponding five-membered substrate **6**. Standard TFA-catalyzed reaction with **1** at room temperature (protocol A) led to a low conversion. We could obtain the desired product **24a** with optimized protocols B and C by adding an additional portion of **1**. In general, six-membered alkenes were less active than the corresponding five-membered ones, and protocol A did not work well for them. We used mostly protocols B and C with an additional amount of reagent **1** or even protocol D. Only active alkenes **38** and **40** bearing two electron-withdrawing substituents (trifluoromethyl and sulfone) gave the desired bicyclic pyrrolidines **38a** and **40a** in 81–98% yield under the standard TFA catalysis. Seven-membered alkene **41** also gave the desired product **41a** in 49% yield under LiF-optimized conditions.

It is worth noting that among all tested alkenes, six-membered compound **26** (push–pull resonance form possible) was the least active (Scheme 1). The reaction was incomplete even with protocol D (LiF, 140 °C, 12 h), and an additional portion of reagent **1** was required. Other protocols A–C did not work for **26** at all. Isomeric alkene **31** and six-membered trifluoromethyl-substituted alkenes **34** and **37** also showed reduced activity.

In terms of medicinal chemistry perspective, the obtained substrates **2a–41a** have large potential. Among them were interesting sulfones (**3a**, **4a**, **5a**, **20a**, **21a**) and monofluoro- (**7a**, **30a**, **35a**), difluoro- (**25a**), and trifluoromethyl-substituted molecules (**17a**, **18a**, **34a**, **35a**). Fluorine-substituted building blocks play in important role in drug discovery and agrochemistry.[17] During elaboration of the reaction scope, we also tried isomeric and homologous molecules. For example, oxygen-containing five-membered isomers **9a** and **12a**, oxygen-containing six-membered isomers **28a**, **29a**, and **31a**, sulfones **20a** and **21a**, and sulfones **38a** and **40a** were synthesized. Indeed, for medicinal chemistry projects during structure–activity relationship (SAR) studies, it is important to use stepwise modifications of an active compound, for example, by using homologous and/or isomeric building blocks, following a minimum modification principle.[18]

Mechanism. A general mechanism for the formation of the nonstabilized azomethyne ylide from reagent **1** was reported before.[14,15] However, to provide readers with the corresponding background, a brief summary is given below. Compound **1** under acidic conditions (TFA, CH_2Cl_2) forms protonated intermediate ***I*-1** that eliminates MeOTMS and gives the azomethyne ylide (Scheme 2).[14] The latter reacts electron-

Scheme 2. Reaction Mechanism



deficient endocyclic alkenes via [3 + 2]-cycloaddition to afford the needed bicyclic pyrrolidines. Reaction of reagent **1** with LiF is believed to proceed via a concerted mechanism: polarized fluorine atom (δ^-) attacks silicon, while polarized lithium atom (δ^+) coordinates with methoxy group as a Lewis acid (Scheme 2).[15] Elimination of TMSF and LiOMe gives the azomethyne ylide that participates next in [3 + 2]-cycloaddition with electron-deficient alkenes.

Activity of Substrates. Some aspects of the activity of alkenes were briefly mentioned above. Here, we summarize some trends that we observed:

(a) Activity of alkenes decreased with the increase of the ring size (Figure 3). Four-membered alkenes were the most active, and protocol A (TFA, rt) could be used. Five-membered alkenes were less active, and protocol B (TFA, rt, slow addition of **1**) and C (LiF, CH_3CN, reflux) were required.

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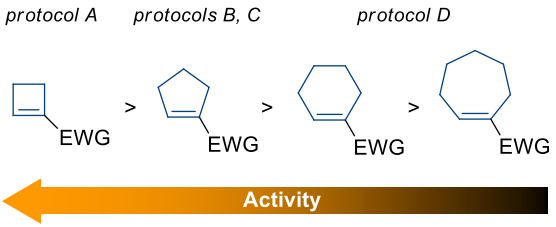

Figure 3. Influence of ring size on the activity of alkenes in [3 + 2]-cycloaddition with azomethine ylide precursor **1**.

Six and seven-membered substrates were the least active. In many cases, only protocol D (LiF, 140 °C, 12 h) worked.

For example, while CF_3-substituted five-membered alkene **17** reacted with **1** already under conditions of protocol A (TFA, rt), the homologous six-membered alkenes **34** and **37** did not react under these conditions. In both cases, protocol D (LiF, 140 °C, 12 h) was required (Scheme 1).

(b) Activity of alkenes decreased upon conjugation of the double bond with oxygen atom. For example, among three substrates **9**, **10**, and **12**, alkene **10** was the most active. Distal oxygen atom was not included in the conjugation with the C=C double bond, and it even additionally activated it by and (−*I*)-inductive effect. Alkene **12** was less active than **10**. Compound **12** could be represented by an inactive resonance form (Figure 4), where oxygen atom is conjugated with a C=C bond. Alkene **9** possessed the lowest activity because its structure could be shown by push−pull resonance form where the oxygen atom, C=C bond, and ester group are all involved in the conjugation (Figure 4, Table 1). The same trend was observed in six-membered substrates **26**, **28**, **29**, and **31**.

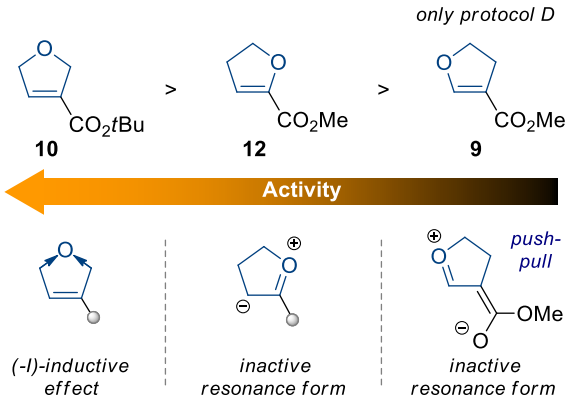

Figure 4. Influence of the position of O-atom in the ring on the activity of alkenes in [3 + 2]-cycloaddition with azomethine ylide precursor **1**.

(c) The activity of alkenes increased with higher electron-withdrawing ability (EWG) of the substituent. For example, within alkenes **15**−**17**, compound **16** showed the highest activity (Figure 5). Alkene **15** with a nitrile group was slightly less active. The trifluoromethyl substituent has lower electron-withdrawing ability than both nitrile and ester groups.[19] Therefore, alkene **17** was the least active. The same trend was observed in six-membered substrates. For example, while alkenes **32** and **33** with a CO_2Me group reacted with **1** using protocol C (LiF, CH_3CN, reflux), the CF_3 analogue **34** gave no product under these conditions. Only with protocol D (LiF, 140 °C, 12 h) was the corresponding fluorinated bicycle **34a** obtained (Scheme 1).

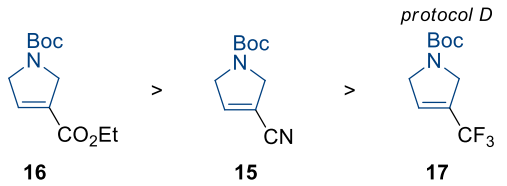

Figure 5. Influence of the EWG group on the activity of alkenes in [3 + 2]-cycloaddition with azomethine ylide precursor **1**.

In summary, among all tested cyclic alkenes (Scheme 1), the least active ones were (a) "push−pull" alkenes **9**, **26**, and **31** and (b) six-membered CF_3-alkenes **34** and **37**. Attempted cycloaddition of these alkenes with reagent **1** under the reported conditions failed. Only protocol D (LiF, 140 °C, 12 h) developed in this work provided the needed bicyclic products.

Modifications. The substrates depicted in Scheme 1 cannot be directly used in medicinal chemistry projects because they have N- and C-protecting groups. Therefore, we performed some representative transformations to convert them into the desired building blocks. For example, [Pd]-catalyzed hydrogenation of the *N*-benzyl bond in pyrrolidine **25a**, *N*-Boc protection, and alkali hydrolysis of the ester group gave an interesting fluorinated bicyclic *β*-proline **25b** (Scheme 3).[20] The synthesis was performed on 20 g scale. Using this three-step strategy, we easily synthesized several interesting bicyclic *β*-prolines depicted on Scheme 3. Among them were fluorine-containing amino acids **7b**, **25b**, and **30b**,[21] sulfone-substituted amino acids **23b** and **39b**, and numerous isomeric/homologue oxygen- and nitrogen-containing bicyclic *β*-prolines.

Cleavage of the *N*-benzyl group in compound **19a** with [Pd]-catalyzed hydrogenation gave bicyclic *α*-proline analogue **19c** in 77% yield (Scheme 4). A similar tactic was used to obtain other bicyclic *NH*-free pyrrolidines as shown in Scheme 4. Among them were bicyclic sulfones **3c**−**5c**, **20c**, **21c**, **38c**, and **40c**, fluorine-containing pyrrolidine **35c**, and unique bis-trifluoromethyl-substituted diamine **18c**.

Alkali hydrolysis of the ester group in **29a**, Curtius reaction with *tert*-butyl alcohol, and hydrogenative cleavage of the *N*-benzyl group gave bicyclic diamine **29d** in 37% combined yield (Scheme 5). Following that three-step tactic, other diamines **2d**, **6d**, **7d**, **23d**−**25d**, and **28d** were easily synthesized. All syntheses were performed on a gram scale. Among the products were fluorine-containing diamine **7d**, difluoro-substituted diamine **25d**, and sulfone-containing diamine **23d**.

Reduction of the ester group in compound **7a** with $LiAlH_4$ and the standard cleavage of the *N*-benzyl moiety gave the fluorine-substituted amino alcohol **7e** in 73% combined yield (Scheme 6). Analogously, three bicyclic amino alcohols **2e**, **6e**, and **24e**, two nitrogen-containing amino alcohols **14e** and **32e**, and five oxygen-containing alcohols **10e**, **12e**, and **26e** were rapidly prepared.

Several other representative modifications were performed as well. Reduction of nitrile **15a** with $LiAlH_4$, *N*-Boc protection, and cleavage of the *N*-benzyl bond gave diamine **15f** in 64% yield (Scheme 6). An analogous sequence of steps was performed with nitrile **27a** to produce diamine **27f** in 68% combined yield (Scheme 7). Amino alcohol **9e** was *N*-Boc protected, *O*-alkylated with methyl iodide, and *N*-deprotected to afford bicyclic amine **9g** in 71% combined yield (Scheme 7). From amino alcohol **12**, analogous derivative **12g** was also

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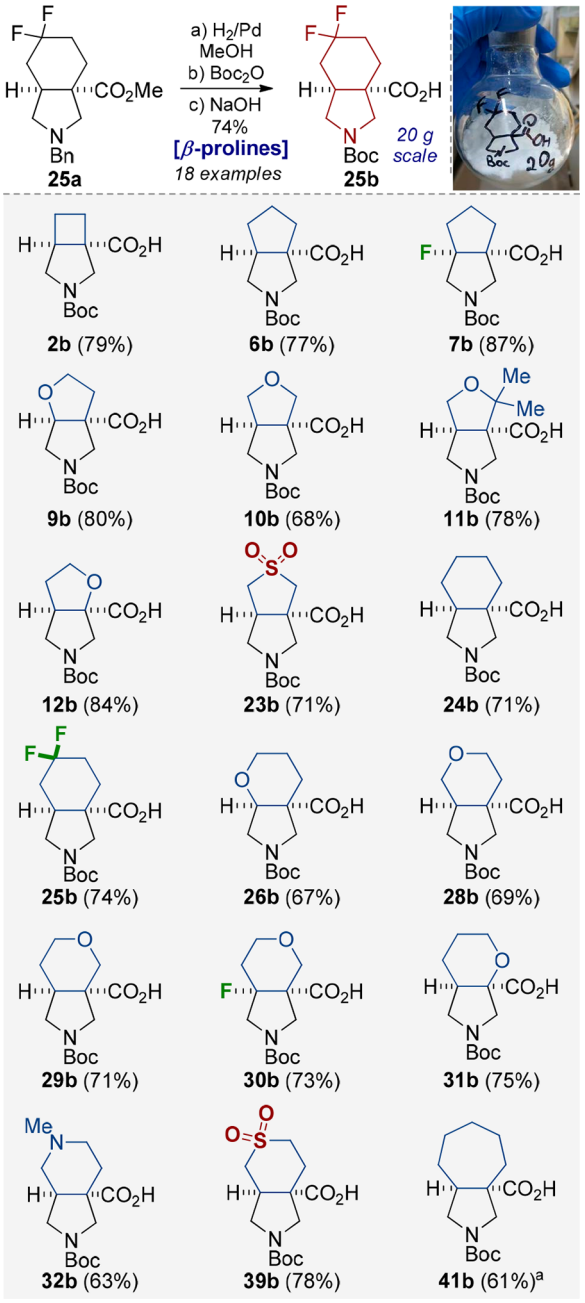
Scheme 3. Synthesis of Bicyclic Amino Acid–β-Prolines[a]

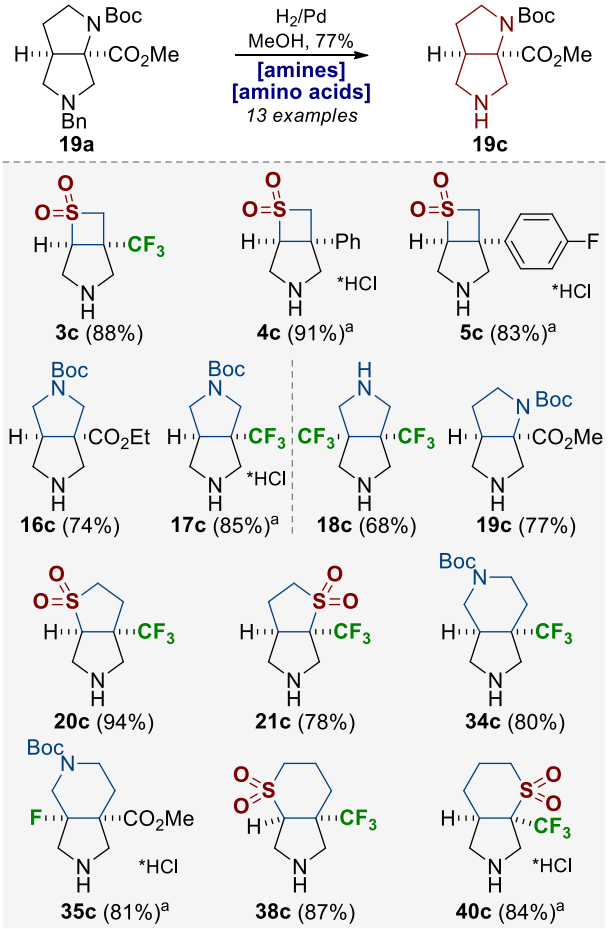


[a]Synthesis was performed from nitrile **41a**: (a) NaOH; (b) H_2/Pd, MeOH; (c) Boc_2O.

obtained. Representative heterocyclization of the carboxylic group in **10b** compound gave oxadiazole **10h** (Scheme 7).

Finally, it is important to add that in some cases an external electron-withdrawing group (EWG) was not needed for the [3 + 2]-cycloaddition. First, we were also surprised to see that four-membered alkene **42** having no EWG reacted with compound **1** in the presence of LiF in acetonitrile to afford the needed bicyclic azetidine **42a** in 12% yield.[22] Presumably, the driving force of that reaction was the strained structure of the starting four-membered alkene.[23] Under analogous conditions, five-membered alkene **43** and six-membered alkene **44** did not react, however (Scheme 8).

Scheme 4. Synthesis of Bicyclic Pyrrolidine-Containing Amines and Amino Acids[a]



[a]1 M HCl in dioxane was added after the reaction.

In addition, the [3 + 2]-cycloaddition of reagent **1** proceeded with alkenes that already contained the electron-withdrawing moiety in the cycle (Scheme 9). For example, cyclic sulfones **45** and **46** smoothly reacted with **1** under TFA catalysis (**45**, protocol A) or under LiF catalysis (**46**, protocol C).[24] Six-membered substrate **47** was less active, and only ca. 50% conversion was observed with standard protocol C. Therefore, an additional portion of reagent **1** was added after 48 h to finish the transformation. The corresponding bicyclic products **45a–47a** were obtained in 70–84% yield. Cleavage of the *N*-Bn group with [Pd]-catalyzed hydrogenation provided bicyclic sulfone-containing pyrrolidines **45c–47c** in 90–95% yield.

Applications. A practical [3 + 2]-cycloaddition approach to fused pyrrolidines developed in this work allowed not only preparation of novel compounds but also dramatically simplified synthesis of the existing ones. For example, compound **48** (DS21412020) was discovered in 2018 by Daiichi Sankyo scientists as a promising antibacterial agent.[25] The authors synthesized key diamine intermediate **29d** in 13 steps from acid **49** (Scheme 10). Our approach allowed for the rapid preparation of diamine **29d** on a 10 g scale in only four steps from alkene **29** (Schemes 5 and 10).

In 2007, Abbott chemists reported on the discovery of novel agent against dementia, sofinicline.[26] Synthesis of the key diamine **50** was undertaken from amine **51** in 12 steps

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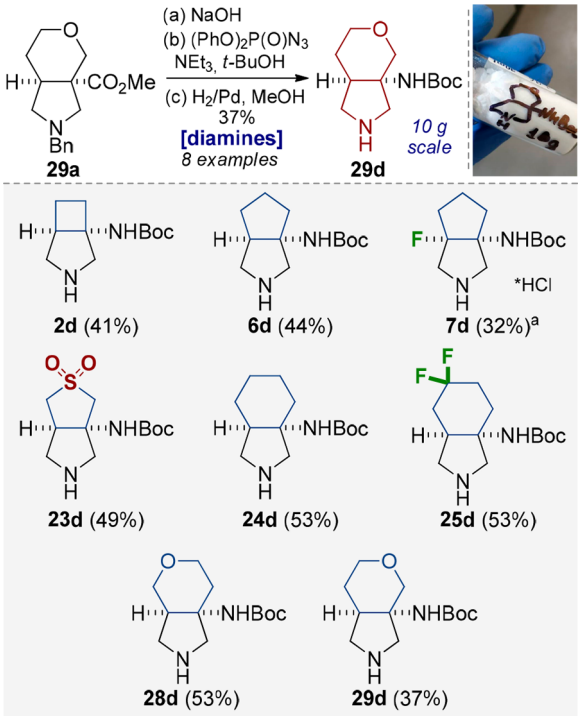
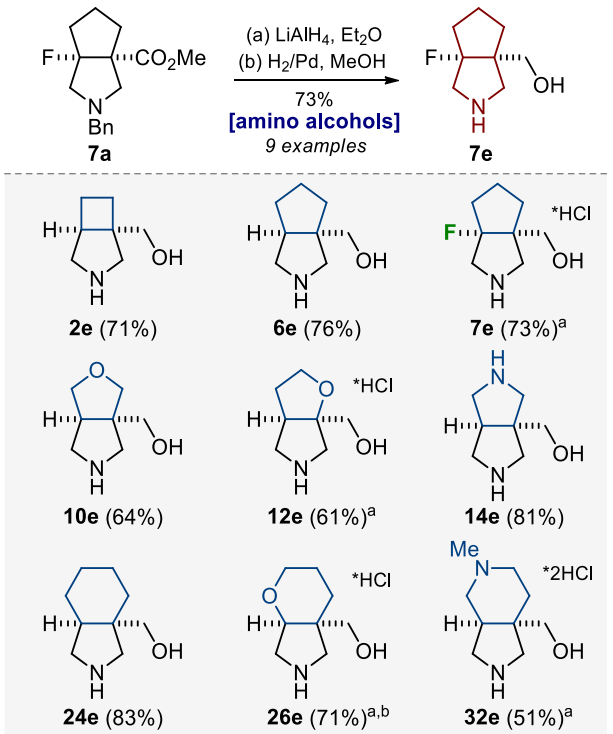
Scheme 5. Synthesis of Bicyclic Pyrrolidine-Containing Diamines[a]



[a]1 M HCl in EtOAc was added after the reaction.

Scheme 6. Synthesis of Bicyclic Pyrrolidine-Containing Amino Alcohols[a,b]

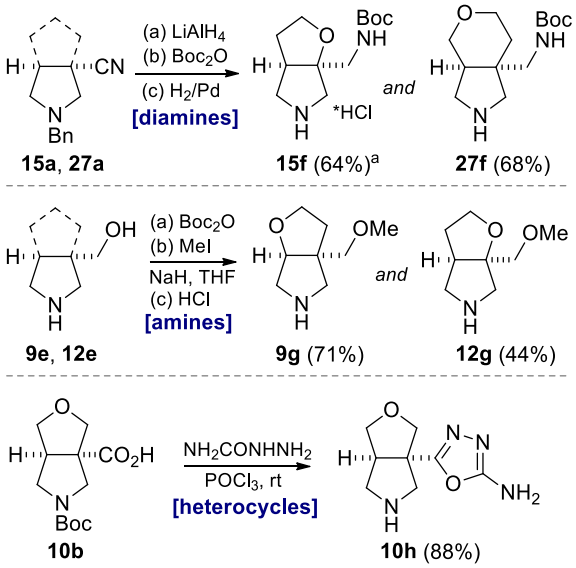


[a]1 M HCl in dioxane was added after the reaction. [b]Reduction was performed with $NaBH_4$/LiCl in THF/EtOH.

(Scheme 10). Our [3 + 2]-cycloaddition strategy allowed preparation of diamine **50** in milligram quantities from the commercially available *N*-Boc azetidinol (**52**) in only four steps.

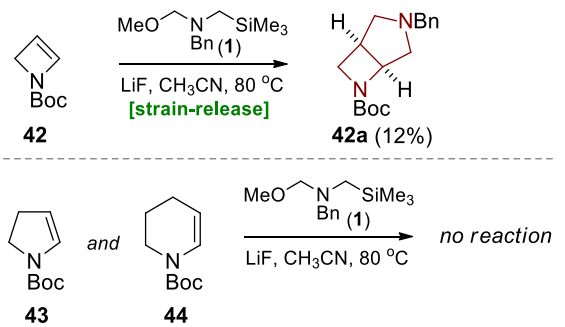
In 2016, chemists from ARIAD Pharmaceuticals reported on the discovery of brigatinib, a potent, orally active inhibitor of anaplastic lymphoma kinase (Scheme 10).[27] In 2017, it was approved by the FDA as an anticancer drug. Since that time,

Scheme 7. Synthesis of Diamines 15f and 27f, OMe-pyrrolidines 9g and 12g, and Oxadiazole 10h[a]

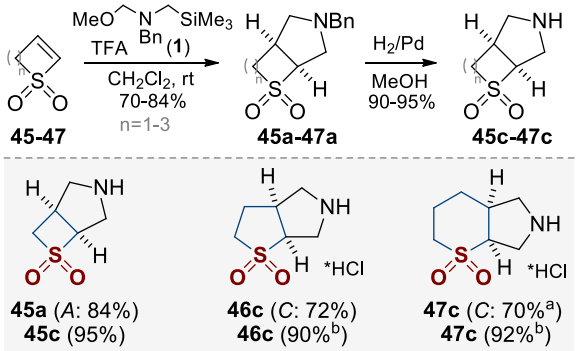


[a]1 M HCl in EtOAc was added.

Scheme 8. Attempted [3 + 2]-Cycloaddition of Enamides 42-44



Scheme 9. [3 + 2]-Cycloaddition of Sulfones 45−47 with 1[a,b]



[a]Additional portion of **1** was added after 48 h. [b]1 M HCl in dioxane was added after the reaction.

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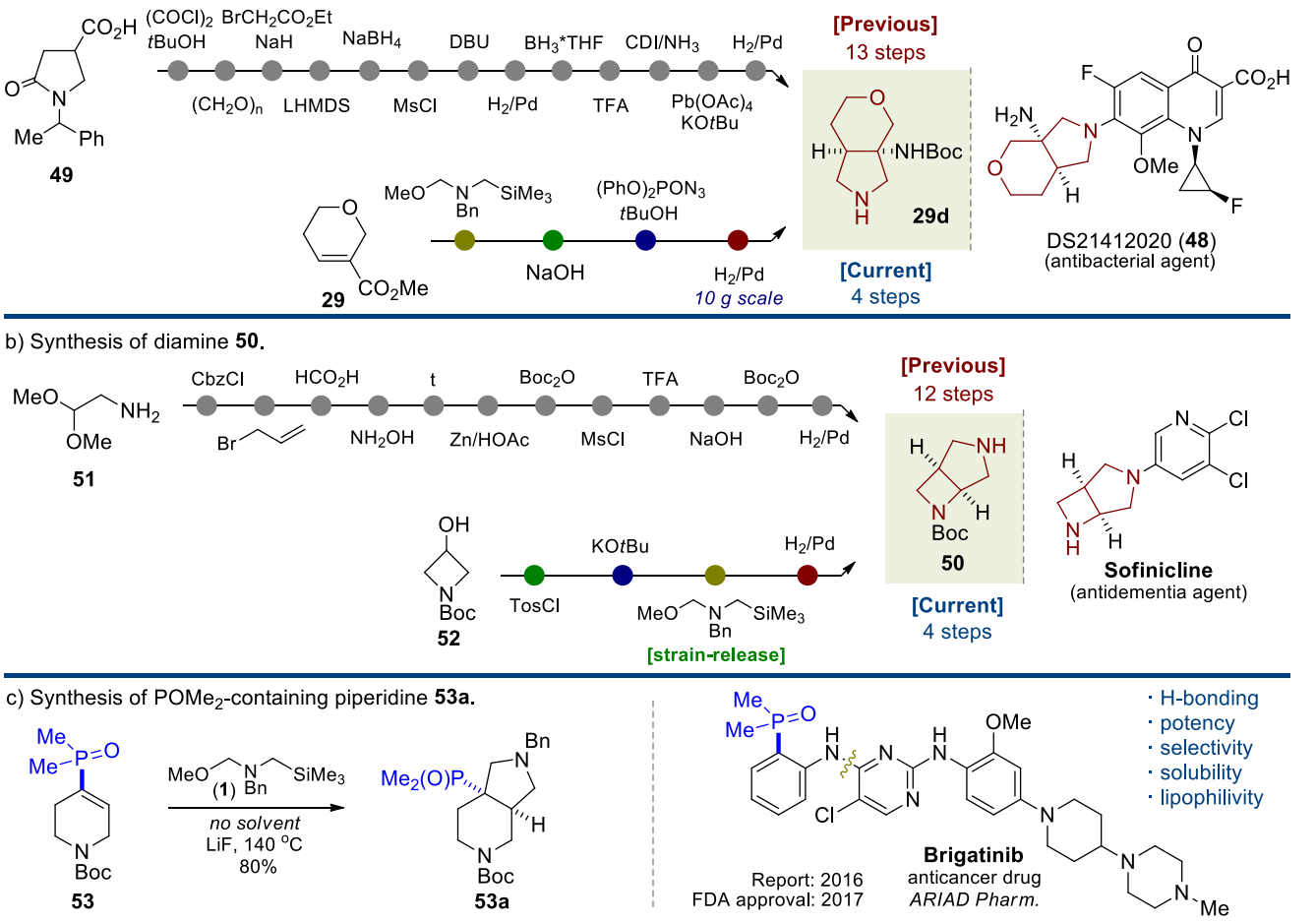
Scheme 10. Synthesis of Bicyclic Pyrrolidines 29d and 50 (Literature Approach vs This Work) and Bicyclic $POMe_2$-Substituted Piperidine 53a



$P(O)Me_2$-substituted building blocks immediately became popular in medicinal chemistry.[28] In this context, we performed the [3 + 2]-cycloaddition of alkene **53** with reagent **1**. Under the conditions of protocol D (LiF, 140 °C, 12 h), the needed bicyclic $P(O)Me_2$-containing pyrrolidine was isolated in 80% yield. Systematic study on the preparation of various $P(O)Me_2$-pyrrolidines via [3 + 2]-cycloaddition is ongoing and will be reported later.

Basicity of Amines. As it was mentioned before, during elaboration of scope of [3 + 2]-cycloaddition (Scheme 1), we tried to prepare isomeric/homologous molecules. The latter are especially interesting for medicinal chemistry applications. For example, compounds with basic aliphatic nitrogen atom often cause toxicity due to affinity to HERG-channel.[29] Therefore, medicinal chemists usually try to fine-tune nitrogen basicity by introducing various electron-deficient substituents at different positions of a molecule.[30]

We also wanted to show how diverse substituents at bicyclic pyrrolidines affected basicity of the nitrogen atom. Indeed, incorporation of fluorine atom into **6c** and pyrrolidine **7c** reduced the basicity by more than one order magnitude: pK_a (**6c**·HCl) = 9.2, pK_a (**7c**·HCl) = 7.6 (Figure 6). Pyrrolidine **23c** with a sulfone group was more than three magnitudes of order less basic than **6c**: pK_a (**23c**·HCl) = 6.1. Incorporation of oxygen atom into pyrrolidine **6c** also reduced basicity in different extent depending on the position: pK_a (**9c**·HCl) = 7.8; pK_a (**10c**·HCl) = 8.2; pK_a (**12c**·HCl) = 7.6. Indeed, this effect was less pronounced in pyrrolidine **10c** because oxygen and nitrogen atoms are separated by four single bonds. In pyrrolidines **9c** and **12c**, however, oxygen and nitrogen atoms are separated by three single bonds only.

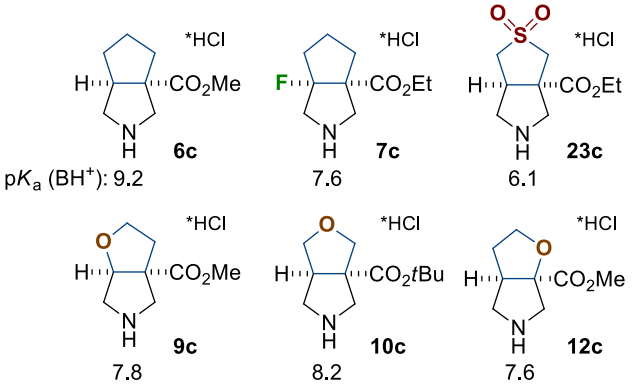


Figure 6. Experimental pK_a values of conjugated acids of amines **6c**, **7c**, **9c**, **10c**, **12c**, and **23c**.

CONCLUSION

Pyrrolidine is one of the most frequently used secondary amines in drug discovery. The structures of more than 50

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drugs contain the pyrrolidine motif. In this work, we developed a general protocol to medchem-relevant fused pyrrolidines via [3 + 2]-cycloaddition between reagent **1** and electron-deficient endocyclic alkenes. Known conditions for generation of the azomethyne ylide from compound 1—protocol A (TFA, rt) and protocol C (LiF, acetonitrile, reflux)—worked well for [3 + 2]-cycloaddition of activated four- and five-membered alkenes (Scheme 1). For less active substrates, more effective protocol B (TFA, rt, slow addition of **1**) was elaborated. Unexpectedly, push−pull alkenes **9**, **26**, and **31** and six-membered CF_3-substituted **34** and **37** failed to react with **1** under all previously reported conditions (Scheme 1, Table 1). Therefore, in this work we developed superior protocol D (LiF, 140 °C, 12 h) and could also convert these substrates into the corresponding bicyclic pyrrolidines **9a**, **26a**, **31a**, **34a**, and **37a**. The synthesis of most products was performed on a 5−30 g scale. From the [3 + 2]-cycloaddition adducts **2a**−**41a**, unique building blocks for medicinal chemistry—amino acids, diamines, amino alcohols, amines, and β-prolines—were easily synthesized (Schemes 2−8). Among the obtained compounds were medchem-relevant sulfones, monofluoro-, difluoro-, and trifluoromethyl-substituted derivatives. Importantly, the developed approach not only led to the practical preparation of novel compounds but also significantly simplified the synthesis of existing ones (Scheme 10). Also, after discovery of the anticancer drug brigatinib (Scheme 10), $P(O)Me_2$-substituted compounds have been gaining popularity in medicinal chemistry. Therefore, here we also synthesized the first representative $P(O)Me_2$-substituted bicyclic pyrrolidine **53a** via [3 + 2]-cycloaddition (Scheme 10).

We believe that with the results described here scientists will soon use diverse bicyclic pyrrolidines routinely in medicinal chemistry.

EXPERIMENTAL SECTION

General Considerations. All chemicals were provided by Enamine, Ltd. (www.enamine.net). All solvents were treated according to standard methods. All reactions were monitored by thin-layer chromatography (TLC) and were visualized using UV light. Product purification was performed using silica gel column chromatography. TLC characterization was performed with precoated silica gel GF254 (0.2 mm), while column chromatography characterization was performed with silica gel (100−200 mesh). ^{1}H NMR spectra were recorded at 400, 500, or 600 MHz (Varian); ^{19}F NMR spectra were recorded at 376 MHz (Varian), and ^{13}C NMR spectra were recorded at 100, 126, or 151 MHz (Varian). ^{1}H NMR chemical shifts are calibrated using residual undeuterated solvents $CHCl_3$ (δ = 7.26 ppm) or DMSO (δ = 2.50 ppm). ^{13}C NMR chemical shifts for ^{13}C NMR are reported relative to the central $CHCl_3$ (δ = 77.16 ppm) or DMSO (δ = 39.52 ppm). Coupling constants are given in hertz. High-resolution mass spectra (HRMS) were recorded on an Agilent LC/MSD TOF mass spectrometer by electrospray ionization time-of-flight reflectron experiments.

Protocol A (2a as an Example). *Methyl 3-Benzyl-3-azabicyclo-[3.2.0]heptane-1-carboxylate (**2a**).* To a stirred solution of **2** (11.20 g, 0.1 mol, 1.0 equiv) and CF_3COOH (1.14 g, 0.01 mol, 0.1 equiv) in CH_2Cl_2 (500 mL) was added **1** (28.44 g, 0.12 mol, 1.2 equiv) dropwise. The temperature was maintained in the range of 20−35 °C by the occasional cooling of the reaction flask in an ice−water bath. The mixture was stirred for 12 h at rt. The mixture was neutralized with a saturated solution of $NaHCO_3$. The organic layer was washed with brine (1 × 200 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc = 9:1). Yield: 23.52 g, 0.096 mol, 96%, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (d, J = 7.5 Hz, 2H), 7.35 (t, J = 7.4 Hz, 2H), 7.28 (d, J = 5.7 Hz, 1H), 3.74 (s, 2H), 3.73 (s, 3H), 2.99 (d, J = 8.7 Hz, 2H), 2.87 (d, J = 9.2 Hz, 1H), 2.56−2.43 (m, 1H), 2.40 (d, J = 9.2 Hz, 1H), 2.30 (dd, J = 8.7, 6.0 Hz, 2H), 2.23−2.04 (m, 2H), 1.88−1.74 (m, 1H) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 176.2, 139.6, 128.7, 128.3, 127.0, 62.3, 60.3, 59.6, 51.9, 51.8, 41.9, 27.6, 21.9 ppm. LCMS (M + H)$^+$: 246. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{15}H_{20}NO_2$ 246.1494; found 246.1480.

Protocol B (6a as an Example). *Methyl 2-Benzylhexahydro-cyclopenta[c]pyrrole-3a(1H)-carboxylate (**6a**).* To a stirred solution of **6** (12.50 g, 0.1 mol, 1.0 equiv) and **1** (4.75 g, 0.02 mol, 0.2 equiv) in CH_2Cl_2 (500 mL) was added CF_3COOH (1.14 g, 0.01 mol, 0.1 equiv) dropwise. The temperature was maintained in the range of 20−30 °C by the occasional cooling of the reaction flask in an ice−water bath. Then a second portion of **1** (23.70 g, 0.1 mol, 1.0 equiv) was slowly added dropwise (over 2 h) to the mixture. The mixture was stirred overnight at room temeperature. The mixture was neutralized with a saturated solution of $NaHCO_3$. The organic layer was washed with brine (1 × 200 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc = 8:2). Yield: 19.94 g, 0.077 mol, 77%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38−7.20 (m, 5H), 3.70 (s, 3H), 3.58 (q, J = 13.2 Hz, 2H), 2.95 (d, J = 9.3 Hz, 1H), 2.93−2.84 (m, 1H), 2.70 (t, J = 8.2 Hz, 1H), 2.47 (d, J = 9.3 Hz, 1H), 2.34 (dd, J = 8.8, 4.1 Hz, 1H), 2.04 (dd, J = 11.8, 6.6 Hz, 1H), 1.95−1.61 (m, 4H), 1.59−1.46 (m, 1H) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 177.9, 139.3, 128.6, 128.3, 126.9, 63.8, 61.3, 59.7, 59.7, 52.1, 47.8, 38.4, 33.6, 26.9 ppm. LCMS (M + H)$^+$: 260. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{16}H_{22}NO_2$ 260.1651; found 260.1644.

Protocol C (14a as an Example). *Methyl 2,5-Dibenzylhexa-hydropyrrolo[3,4-c]pyrrole-3a(1H)-carboxylate (**14a**).* Compound **1** (28.44 g, 0.12 mol, 1.2 equiv) and LiF (9.36 g, 0.36 mol, 3.0 equiv) were added to a solution of **14** (21.70 g, 0.1 mol, 1.0 equiv) in CH_3CN (500 mL), and the mixture was stirred at reflux in an oil bath with a thermocouple during 12 h. When ^{1}H NMR spectroscopy indicated that the reaction was complete, the solvent was evaporated under reduced pressure, and the residue was dissolved in EtOAc (500 mL). The mixture was washed with a 10% cold solution of K_2CO_3 (2 × 100 mL), a saturated aqueous solution of $CuSO_4$ (3 × 100 mL) and brine (1 × 100 mL). The organic phase was separated and dried over Na_2SO_4, and the solvent was evaporated. The crude product was purified by flash chromatography in a mixture of hexanes/EtOAc = 8:2. Yield: 16.45 g, 0.047 mol, 47%, brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39−7.24 (m, 10H), 3.71 (s, 3H), 3.64 (q, J = 13.2 Hz, 4H), 3.13−3.03 (m, 1H), 2.94 (d, J = 9.1 Hz, 2H), 2.79 (t, J = 8.1 Hz, 2H), 2.58 (d, J = 9.2 Hz, 2H), 2.46 (dd, J = 8.7, 4.5 Hz, 2H) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 176.2, 139.1, 128.6, 128.3, 127.0, 62.6, 59.7, 59.4, 59.3, 52.3, 46.7 ppm. LCMS (M + H)$^+$: 351. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{22}H_{27}N_2O_2$ 351.2073; found 351.2065.

Protocol D (9a as an Example). *Methyl 5-Benzylhexahydro-3aH-furo[2,3-c]pyrrole-3a-carboxylate (**9a**).* Compound **9** (12.80 g, 0.1 mol, 1.0 equiv) and **1** (47.40 g, 0.2 mol, 2.0 equiv) were mixed with LiF (7.80 g, 0.3 mol, 3.0 equiv) in a three-necked round-bottom flask equipped with a magnetic stir bar, thermometer, and condenser. The mixture was heated to 140−150 °C for 12 h and then 12 h at 100−110 °C in an oil bath with a thermocouple. The conversion was checked by NMR. After full conversion, the mixture was cooled to room temperature, and acetone (200 mL) was added to the mixture. The mixture was filtered and concentrated under reduced pressure. The residue was purified by column chromatography (gradient, $CHCl_3/CH_3CN$, 9:1 to 7:3) and distillation. Yield: 22.19 g, 0.085 mol, 85%, yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.34−7.11 (m, 5H), 4.55 (d, J = 5.0 Hz, 1H), 3.95 (dd, J = 14.5, 6.7 Hz, 1H), 3.74 (dd, J = 14.3, 6.5 Hz, 1H), 3.65 (s, 3H), 3.52 (s, 2H), 2.77 (d, J = 9.3 Hz, 1H), 2.73 (d, J = 10.3 Hz, 1H), 2.61 (d, J = 9.3 Hz, 1H), 2.35 (dd, J = 10.2, 5.3 Hz, 1H), 2.29−2.19 (m, 1H), 1.94 (dt, J = 12.3, 6.2 Hz, 1H) ppm. ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 174.5, 138.5, 128.3, 128.2, 126.9, 85.3, 68.6, 61.8, 60.4, 59.0, 58.5, 52.2, 39.5 ppm.

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LCMS (M + H)$^+$: 262. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{15}H_{20}NO_3$ 262.1443; found 262.1437.

*3-Benzyl-1-(trifluoromethyl)-6-thia-3-azabicyclo[3.2.0]heptane 6,6-Dioxide (**3a**).* Protocol A was used. Yield: 29.89 g, 0.098 mol, 98%, colorless solid, mp = 105−106 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42−7.26 (m, 5H), 4.66 (d, J = 4.5 Hz, 1H), 4.41 (dd, J = 13.8, 2.6 Hz, 1H), 4.16 (d, J = 13.7 Hz, 1H), 3.85 (d, J = 13.3 Hz, 1H), 3.72 (d, J = 13.6 Hz, 1H), 3.69 (d, J = 12.1 Hz, 1H), 3.07 (d, J = 9.4 Hz, 1H), 2.61 (dd, J = 11.4, 6.8 Hz, 1H), 2.57 (d, J = 9.4 Hz, 1H) ppm. ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 137.2, 128.7, 128.4, 127.7, 125.5 (q, J = 277.9 Hz), 81.6, 70.7, 57.9, 57.5, 54.3, 41.7 (q, J = 31.0 Hz) ppm. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ −73.1 (s) ppm. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{13}H_{15}F_3NO_2S$ 306.0776; found 306.0764.

*3-Benzyl-1-phenyl-6-thia-3-azabicyclo[3.2.0]heptane 6,6-Dioxide (**4a**).* Protocol A was used. The residue was purified by column chromatography (hexane/EtOAc = 9:1). Yield: 27.23 g, 0.087 mol, 87%, brown solid, mp = 110−112 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45−7.25 (m, 10H), 4.73 (dd, J = 6.5, 2.6 Hz, 1H), 4.46 (d, J = 13.0 Hz, 1H), 4.28 (dd, J = 12.9, 2.8 Hz, 1H), 3.88 (d, J = 13.3 Hz, 1H), 3.76 (d, J = 11.2 Hz, 1H), 3.72 (d, J = 13.3 Hz, 1H), 3.30 (d, J = 9.2 Hz, 1H), 2.66 (dd, J = 11.1, 6.9 Hz, 1H), 2.49 (d, J = 9.2 Hz, 1H) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 140.7, 138.0, 129.2, 128.6, 128.6, 127.8, 127.5, 126.1, 84.6, 76.7, 64.9, 58.3, 54.9, 41.8 ppm. LCMS (M + H)$^+$: 314. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{18}H_{20}NO_2S$ 314.1215; found 314.1210.

*3-Benzyl-1-(4-fluorophenyl)-6-thia-3-azabicyclo[3.2.0]heptane 6,6-dioxide (**5a**).* Protocol A was used. The residue was purified by column chromatography (hexane/EtOAc = 7:3). Yield: 29.46 g, 0.089 mol, 89%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.53−7.46 (m, 2H), 7.41−7.31 (m, 4H), 7.30−7.18 (m, 3H), 4.95 (d, J = 4.6 Hz, 1H), 4.45−4.31 (m, 2H), 3.75 (q, J = 13.7 Hz, 2H), 3.47 (d, J = 11.2 Hz, 1H), 3.35−3.32 (m, 1H), 2.64 (dd, J = 11.1, 7.1 Hz, 1H), 2.28 (d, J = 9.1 Hz, 1H) ppm. ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 161.3 (d, J = 244.0 Hz), 138.1, 137.0, 128.6, 128.6, 128.2, 128.2, 126.9, 115.4 (d, J = 21.3 Hz), 83.7, 75.5, 65.3, 57.1, 54.1, 41.0 ppm. LCMS (M + H)$^+$: 332. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{18}H_{19}FNO_2S$ 332.1121; found 332.1104.

*Ethyl 2-benzyl-6a-fluorohexahydrocyclopenta[c]pyrrole-3a(1H)-carboxylate (**7a**).* Modified protocol C was used. Compound **1** (28.44 g, 0.12 mol, 1.2 equiv) and LiF (7.80 g, 0.3 mol, 3.0 equiv) were added to a solution of **7** (14.40 g, 0.1 mol, 1.0 equiv) in CH_3CN (500 mL), and the mixture was stirred at reflux in an oil bath with a thermocouple during 12 h, and an additional portion of **1** (7.11 g, 0.03 mol, 0.3 equiv) was added. When ^{1}H NMR spectroscopy indicated that the reaction was complete, the solvent was evaporated under reduced pressure, and the residue was dissolved in EtOAc (500 mL). The mixture was washed with a 10% cold solution of K_2CO_3 (2 × 100 mL), a saturated aq solution of $CuSO_4$ (3 × 100 mL), and brine (1 × 100 mL). The organic phase was separated and dried over Na_2SO_4, and the solvent was evaporated. The crude product was purified by flash chromatography in a mixture of hexanes/EtOAc/Et_3N = 5:1:0.1. R_f = 0.53. Yield: 19.79 g, 0.068 mol, 68%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56−7.21 (m, 5H), 4.27−4.10 (m, 2H), 3.64 (q, J = 13.1 Hz, 2H), 3.32 (d, J = 9.3 Hz, 1H), 2.96−2.73 (m, 2H), 2.63−2.45 (m, 2H), 2.27−2.05 (m, 1H), 2.04−1.89 (m, 2H), 1.84−1.71 (m, 1H), 1.68−1.54 (m, 1H), 1.29 (t, J = 7.1 Hz, 3H) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 171.8 (d, J = 6.3 Hz), 138.5, 128.3, 128.1, 126.9, 111.2 (d, J = 199.5 Hz), 63.8 (d, J = 28.8 Hz), 62.6, 60.9 (d, J = 17.6 Hz), 60.7, 59.2, 38.3 (d, J = 24.9 Hz), 36.9 (d, J = 0.8 Hz), 24.8 (d, J = 4.3 Hz), 14.0 ppm. ^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$): δ −178.3 (s) ppm. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for: $C_{17}H_{23}FNO_2$ 292.1713; found 292.1720.

*Methyl 2-Benzyl-3a-cyanooctahydrocyclopenta[c]pyrrole-5-carboxylate (**8a**).* Modified protocol C was used. An additional portion of **1** (7.11 g, 0.03 mol, 0.3 equiv) was added after 12 h. The residue was purified by column chromatography (hexane/EtOAc = 7:3). Yield: 14.48 g, 0.051 mol, 51%, yellow oil, d.r. = 1:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36−7.25 (m, 5H), 3.72 (s, 3H), 3.57 (s, 2H), 3.23−3.05 (m, 2H), 2.84 (d, J = 9.5 Hz, 1H), 2.75 (d, J = 9.1 Hz, 1H), 2.71 (d, J = 9.3 Hz, 1H), 2.47 (dd, J = 9.4, 3.2 Hz, 1H), 2.40 (dd, J = 13.1, 9.9 Hz, 1H), 2.26−2.16 (m, 2H), 1.93−1.82 (m, 1H) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 173.9, 138.2, 128.6, 127.4, 124.4, 65.1, 60.9, 59.0, 52.1, 49.6, 44.7, 44.6, 41.9, 36.8. LCMS (M + H)$^+$: 285. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{17}H_{21}N_2O_2$ 285.1603; found 285.1627.

*tert-Butyl 5-Benzyltetrahydro-1H-furo[3,4-c]pyrrole-3a(3H)-carboxylate (**10a**).* Protocol A was used. The oil residue was left in the refrigerator for a few hours to crystallize. The precipitate was then triturated, cooled to the melting point of Et_2O, and filtered. The left residue was concentrated and purified by column chromatography (gradient, hexane/EtOAc, 9:1 to 7:3). Yield: 24.85 g, 0.082 mol, 82%, yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36−7.22 (m, 5H), 4.12 (d, J = 8.8 Hz, 1H), 4.03 (t, J = 8.0 Hz, 1H), 3.66 (d, J = 8.9 Hz, 1H), 3.63−3.53 (m, 3H), 3.11−3.01 (m, 1H), 2.76 (d, J = 9.3 Hz, 1H), 2.66 (d, J = 7.9 Hz, 1H), 2.64 (d, J = 9.0 Hz, 1H), 2.52 (dd, J = 9.1, 3.2 Hz, 1H), 1.44 (s, 9H) ppm ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 173.9, 139.1, 128.5, 128.4, 127.1, 81.1, 77.0, 74.6, 62.3, 61.6, 59.1, 58.8, 48.4, 28.1 ppm. LCMS (M + H)$^+$: 304. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{18}H_{26}NO_3$ 304.1913; found 304.1931.

*Methyl 5-Benzyl-3,3-dimethyltetrahydro-1H-furo[3,4-c]pyrrole-3a(3H)-carboxylate (**11a**).* Protocol C was used. Two additional portions of **1** were added after 12 h (7.11 g, 0.03 mol, 0.3 equiv) and 24 h (7.11 g, 0.03 mol, 0.3 equiv). The residue was purified by column chromatography (hexane/EtOAc = 7:3). Yield: 20.81 g, 0.072 mol, 72%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35−7.22 (m, 5H), 4.03 (t, J = 8.5 Hz, 1H), 3.72 (s, 2H), 3.62 (dd, J = 9.2, 2.9 Hz, 1H), 3.58 (s, 2H), 3.51−3.40 (m, 1H), 3.10 (t, J = 8.5 Hz, 1H), 3.00 (d, J = 9.4 Hz, 1H), 2.58 (d, J = 9.4 Hz, 1H), 2.26 (dd, J = 8.9, 5.1 Hz, 1H), 1.37 (s, 3H), 1.11 (s, 3H) ppm. ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 174.2, 138.9, 128.5, 128.3, 127.1, 82.3, 71.2, 68.0, 61.6, 59.9, 59.6, 52.3, 46.1, 23.6, 23.3 ppm. LCMS (M + H)$^+$: 290. HRMS (ESI-TOF) m/z: [M + H]+ calcd for $C_{17}H_{24}NO_3$ 290.1756; found 290.1762.

*Methyl 5-**b**enzylhexahydro-6aH-furo[2,3-c]pyrrole-6a-carboxylate (**12a**).* Protocol D was used. The residue was purified by column chromatography (hexane/EtOAc = 7:3). Yield: 23.75 g, 0.091 mol, 91%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37−7.21 (m, 5H), 4.20−4.09 (m, 1H), 3.90 (dd, J = 14.9, 7.5 Hz, 1H), 3.77 (s, 3H), 3.72 (d, J = 13.1 Hz, 1H), 3.54 (d, J = 13.1 Hz, 1H), 3.07 (d, J = 10.3 Hz, 1H), 3.00−2.92 (m, 1H), 2.75 (d, J = 10.0 Hz, 1H), 2.73 (d, J = 7.9 Hz, 1H), 2.53 (dd, J = 9.1, 7.0 Hz, 1H), 2.19−2.08 (m, 1H), 1.89−1.79 (m, 1H) ppm. ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 174.1, 138.7, 128.7, 128.4, 127.1, 92.1, 70.5, 63.8, 59.9, 59.4, 52.6, 48.6, 33.5 ppm. LCMS (M + H)$^+$: 262. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{15}H_{20}NO_3$ 262.1443; found 262.1448.

*5-Benzylhexahydro-6aH-furo[2,3-c]pyrrole-6a-carbonitrile (**13a**).* Protocol C. The residue was purified by column chromatography ($CHCl_3$/CH_3CN = 9:1). Yield: 16.64 g, 0.073 mol, 73%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39−7.24 (m, 5H), 4.22−4.10 (m, 1H), 3.90 (td, J = 8.5, 6.3 Hz, 1H), 3.69 (d, J = 13.1 Hz, 1H), 3.56 (d, J = 13.1 Hz, 1H), 3.22 (d, J = 10.6 Hz, 1H), 3.19−3.07 (m, 1H), 2.71 (d, J = 8.4 Hz, 1H), 2.64 (d, J = 10.6 Hz, 1H), 2.54 (dd, J = 9.5, 7.0 Hz, 1H), 2.35−2.19 (m, 1H), 1.93−1.79 (m, 1H) ppm. ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 137.9, 128.7, 128.5, 127.4, 120.4, 82.3, 71.0, 64.4, 59.0, 58.7, 50.6, 33.4 ppm. LCMS (M + H)$^+$: 229. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{14}H_{17}N_2O$ 229.1341; found 229.1324.

*tert-Butyl 5-benzyl-3a-cyanohexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (**15a**).* Protocol C was used. The crude product was purified by chromatography (gradient, hexane/methyl *tert*-butyl ether, 9:1 to 7:3). Yield: 14.39 g, 0.044 mol, 44%, white solid, mp = 100−101 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.37−7.21 (m, 5H), 3.73−3.53 (m, 5H), 3.21 (d, J = 11.3 Hz, 1H), 3.07 (br s, 1H), 2.84 (d, J = 9.6 Hz, 1H), 2.79 (t, J = 8.5 Hz, 1H), 2.67 (d, J = 9.6 Hz, 1H), 2.40−2.29 (m, 1H), 1.40 (s, 9H) ppm. ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6): δ 153.0, 138.1, 128.3, 128.2, 127.0, 123.1, 79.2, 62.2, 58.8, 57.4, 54.2, 50.8, 48.4 (br s), 44.5 (br s), 28.0 ppm. LCMS (M +

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H)$^+$: 328. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{19}H_{26}N_3O_2$ 328.2025; found 328.2020.

*2-tert-Butyl 3a-Ethyl-5-benzyltetrahydropyrrolo[3,4-c]pyrrole-2,3a(1H,3H)-dicarboxylate (**16a**).* Protocol C was used. The residue was purified by column chromatography (hexane/EtOAc = 9:1). Yield: 17.20 g, 0.046 mol, 46%, yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.34−7.20 (m, 5H), 4.09 (q, J = 7.0 Hz, 2H), 3.74 (d, J = 11.4 Hz, 1H), 3.62−3.49 (m, 3H), 3.34 (d, J = 11.4 Hz, 1H), 3.18 (dd, J = 11.0, 3.5 Hz, 1H), 2.95 (br s, 1H), 2.73 (d, J = 9.2 Hz, 1H), 2.69−2.54 (m, 2H), 2.47 (br s, 1H), 1.39 (s, 9H), 1.17 (t, J = 7.1 Hz, 3H) ppm. ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6): δ 173.8, 153.1, 138.6, 128.18, 128.16, 126.8, 78.6, 61.7, 60.7, 59.3, 58.1, 54.6, 51.8 (br s), 45.4 (br s), 28.1, 13.9 ppm. LCMS (M + H)$^+$: 375. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{21}H_{31}N_2O_4$ 375.2284; found 375.2277.

*tert-Butyl 5-Benzyl-3a-(trifluoromethyl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (**17a**).* Protocol D was used. The residue was purified by column chromatography (hexane/EtOAc = 9:1). Yield: 27.75 g, 0.075 mol, 75%, yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33−7.24 (m, 5H), 3.94−3.86 (m, 1H), 3.83−3.68 (m, 1H), 3.61 (s, 2H), 3.43−3.30 (m, 1H), 3.26 (dd, J = 11.0, 4.3 Hz, 1H), 2.87 (br s, 1H), 2.72−2.55 (m, 4H), 1.47 (s, 9H) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 154.0, 138.5, 128.52, 128.49, 127.3, 80.0, 59.7 (br s), 59.4, 59.0, 53.0 (br s), 51.6 (br s), 44.5 (br s), 43.6 (br s), 28.6 ppm. ^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$): δ −74.2 ppm. LCMS (M + H)$^+$: 371. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{19}H_{26}F_3N_2O_2$ 371.1946; found 371.1928.

*2,5-Dibenzyl-3a,6a-bis(trifluoromethyl)octahydropyrrolo[3,4-c]pyrrole (**18a**).* To a stirred solution of **1** (47.40 g, 0.20 mol, 2.0 equiv) in CH_2Cl_2 (500 mL) was added **18** (16.20 g, 0.10 mol, 1.0 equiv) in portions at −40 °C under Ar. Then a solution of CF_3COOH (2.20 g, 0.02 mol, 0.2 equiv) in CH_2Cl_2 (300 mL) was added dropwise at −35 °C. The mixture was stirred at −30 °C for 5 and 7 h at rt. The mixture was neutralized with a saturated solution of $NaHCO_3$. The mixture was stirred for 30 min at rt. The organic layer was separated and washed with brine (4 × 200 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by column chromatography (hexane/EtOAc/2,2,2-trifluoroethanol = 75:15:10) to give the desired product as colorless oil. Yield: 29.96 g, 0.07 mol, 70%. R_f = 0.3. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34−7.22 (m, 10H), 3.63 (s, 4H), 2.96 (d, J = 9.4 Hz, 4H), 2.68 (d, J = 9.1 Hz, 4H) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 138.1, 128.6, 128.4, 127.4, 60.9, 60.0 (br s), 58.5 ppm. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ −68.1 (s) ppm. GCMS (M): 428. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{22}H_{23}F_6N_2$ 429.1765; found 429.1759.

*1-tert-Butyl 6a-Methyl-5-benzylhexahydropyrrolo[3,4-b]pyrrole-1,6a-dicarboxylate (**19a**).* Protocol A was used. The residue was purified by column chromatography (hexane/EtOAc = 9:1). Yield: 19.80 g, 0.055 mol, 55%, yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.44−7.11 (m, 5H), 3.65, 3.60 (2 × s, 3H), 3.54−3.39 (m, 4H), 3.21, 3.09 (2 × d, J = 10.2 Hz, 1H), 2.86−2.67 (m, 2H), 2.49−2.37 (m, 2H), 1.81−1.63 (m, 1H), 1.81−1.63 (m, 1H), 1.37, 1.26 (2 × s, 9H) ppm. ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6): δ 173.0, 152.1, 138.7, 128.2, 128.1, 126.8, 79.1, 78.9, 73.3, 73.0, 62.5, 61.4, 58.3, 58.1, 52.2, 52.1, 49.9, 48.8, 47.5, 47.1, 28.1, 28.0, 27.8 ppm. LCMS (M + H)$^+$: 361. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{20}H_{29}N_2O_4$ 361.2127; found 361.2122.

*5-Benzyl-3a-(trifluoromethyl)hexahydro-2H-thieno[2,3-c]pyrrole 1,1-dioxide (**20a**).* Protocol A was used. The crude product was crystallized from CCl_4. Yield: 26.80 g, 0.084 mol, 84%, colorless crystals, mp = 80−82 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35−7.22 (m, 5H), 3.77 (d, J = 13.1 Hz, 1H), 3.64 (d, J = 10.6 Hz, 1H), 3.50 (d, J = 13.1 Hz, 1H), 3.36 (d, J = 6.3 Hz, 1H), 3.34−3.17 (m, 2H), 2.90 (d, J = 9.6 Hz, 1H), 2.68 (d, J = 9.7 Hz, 1H), 2.63 (dd, J = 10.6, 6.5 Hz, 1H), 2.60−2.49 (m, 1H), 2.29−2.16 (m, 1H) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 137.4, 128.7, 128.4, 127.6, 126.8 (q, J = 279.4 Hz), 62.6, 60.9, 58.6, 56.0, 55.3 (q, J = 27.3 Hz), 50.4, 28.1 ppm. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ −74.8 (s) ppm. GCMS (M): 319. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{14}H_{17}F_3NO_2S$ 320.0932; found 320.0948.

*5-Benzyl-6a-(trifluoromethyl)hexahydro-2H-thieno[2,3-c]pyrrole 1,1-Dioxide (**21a**).* Protocol A was used. Crystallization from EtOAc−*n*-hexane gave pure compound **21a**. Yield: 30.62 g, 0.096 mol, 96%, colorless crystals, mp = 116−117 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46−7.09 (m, 5H), 3.79−3.68 (m, 2H), 3.59 (d, J = 13.1 Hz, 1H), 3.38−3.25 (m, 1H), 3.23−3.06 (m, 2H), 2.77 (d, J = 9.3 Hz, 1H), 2.70 (d, J = 10.8 Hz, 1H), 2.59 (t, J = 7.9 Hz, 1H), 2.43−2.26 (m, 1H), 2.10−1.93 (m, 1H) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 137.7, 128.6, 128.4, 127.5, 124.4 (q, J = 280.0 Hz), 71.8 (q, J = 26.7 Hz), 59.5, 58.6, 56.0, 51.7, 43.6, 25.6 ppm. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ −67.9 (s), −162.2 (s) ppm. GCMS (M): 319. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{14}H_{17}F_3NO_2S$ 320.0932; found 320.0945.

*Methyl 5-Benzyltetrahydro-1H-thieno[3,4-c]pyrrole-3a(3H)-carboxylate (**22a**).* Protocol C was used. The residue was purified by column chromatography (hexane/EtOAc = 9:1). Yield: 11.91 g, 0.043 mol, 43%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33−7.20 (m, 5H), 3.72 (s, 3H), 3.59 (q, J = 13.1 Hz, 2H), 3.40−3.29 (m, 1H), 3.22 (d, J = 12.0 Hz, 1H), 3.15 (d, J = 9.3 Hz, 1H), 3.06 (dd, J = 11.7, 7.1 Hz, 1H), 2.91 (t, J = 8.2 Hz, 1H), 2.76 (d, J = 12.0 Hz, 1H), 2.62 (dd, J = 11.8, 3.8 Hz, 1H), 2.47 (d, J = 9.3 Hz, 1H), 2.36 (dd, J = 8.8, 6.1 Hz, 1H) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 175.5, 138.6, 128.4, 128.2, 127.1, 126.9, 64.3, 62.8, 59.8, 59.1, 52.4, 51.7, 41.8, 38.4 ppm. LCMS (M + H)$^+$: 278. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{15}H_{20}NO_2S$ 278.1215; found 278.1208.

*Ethyl 5-Benzyltetrahydro-1H-thieno[3,4-c]pyrrole-3a(3H)-carboxylate 2,2-Dioxide (**23a**).* Protocol A was used. The residue was purified by column chromatography (hexane/EtOAc = 9:1). Yield: 26.16 g, 0.081 mol, 81%, yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.44−7.10 (m, 5H), 4.14 (q, J = 7.0 Hz, 2H), 3.67−3.63 (d, J = 14.0 Hz, 1H), 3.64 (d, J = 13.3 Hz, 1H), 3.56 (d, J = 13.3 Hz, 1H), 3.49−3.38 (m, 1H), 3.35−3.26 (m, 1H), 3.22 (d, J = 14.0 Hz, 1H), 2.97 (dd, J = 13.4, 7.6 Hz, 1H), 2.78 (d, J = 9.5 Hz, 1H), 2.71 (d, J = 9.0 Hz, 1H), 2.68 (d, J = 9.3 Hz, 1H), 2.59 (dd, J = 9.2, 3.6 Hz, 1H), 1.19 (t, J = 7.1 Hz, 3H) ppm. ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 172.5, 138.3, 128.2, 127.0, 62.8, 61.4, 58.4, 57.4, 55.4, 53.6, 53.5, 40.4, 13.9 ppm. LCMS (M + H)$^+$: 324. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{16}H_{22}NO_4S$ 324.1270; found 324.1291.

*Methyl 2-Benzyloctahydro-3aH-isoindole-3a-carboxylate (**24a**).* Protocol C was used. Two additional portions of **1** were added after 12 h (7.11 g, 0.03 mol, 0.3 equiv) and 24 h (7.11 g, 0.03 mol, 0.3 equiv). The residue was purified by column chromatography (hexane/EtOAc = 9:1). Yield: 22.66 g, 0.083 mol, 83%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39−7.20 (m, 5H), 3.80−3.73 (m, 2H), 3.70 (s, 3H), 2.96 (d, J = 9.4 Hz, 1H), 2.84−2.67 (m, 3H), 2.04−1.90 (m, 1H), 1.82−1.66 (m, 2H), 1.61−1.22 (m, 5H) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 176.9, 139.5, 128.7, 128.3, 127.0, 62.4, 60.6, 57.0, 52.0, 51.3, 39.0, 30.6, 25.4, 22.4, 21.4 ppm. LCMS (M + H)$^+$: 274. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{17}H_{24}NO_2$ 274.1807; found 274.1822.

*Methyl 2-Benzyl-6,6-difluorooctahydro-3aH-isoindole-3a-carboxylate (**25a**).* Protocol B was used. An additional portion of **1** (7.11 g, 0.03 mol, 0.3 equiv) was added after 12 h. The residue was purified by column chromatography (hexane/EtOAc = 9:1). Yield: 23.48 g, 0.076 mol, 76%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34−7.23 (m, 5H), 3.73 (s, 3H), 3.71−3.66 (m, 2H), 2.99 (d, J = 9.7 Hz, 1H), 2.96−2.89 (m, 1H), 2.85−2.75 (m, 2H), 2.74 (d, J = 9.7 Hz, 1H), 2.22−2.10 (m, 2H), 2.09−1.96 (m, 3H), 1.95−1.79 (m, 1H) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 175.9, 139.2, 128.6, 128.4, 127.1, 123.7 (t, J = 241.0 Hz), 62.0, 60.1, 57.5, 52.4, 50.4, 38.5 (t, J = 4.4 Hz), 33.5 (t, J = 24.1 Hz), 30.9 (t, J = 24.8 Hz), 28.1 ppm. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ −90.4 − −92.6 (m) ppm. LCMS (M + H)$^+$: 310. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{17}H_{22}F_2NO_2$ 310.1619; found 310.1611.

*Methyl 6-Benzylhexahydropyrano[2,3-c]pyrrole-4a(2H)-carboxylate (**26a**).* Protocol D was used. An additional portion of **1** (7.11 g, 0.03 mol, 0.3 equiv) was added after 12 h. The residue was purified by column chromatography (hexane/EtOAc = 8:2). Yield: 17.33 g, 0.063 mol, 63%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34−7.21 (m, 5H), 4.37 (d, J = 5.1 Hz, 1H), 3.95−3.85 (m, 1H), 3.73 (s, 3H), 3.72

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(s, 2H), 3.43 (td, J = 11.1, 3.6 Hz, 1H), 3.17 (dd, J = 10.8, 5.4 Hz, 1H), 3.01 (d, J = 8.9 Hz, 1H), 2.83 (d, J = 8.9 Hz, 1H), 2.61 (d, J = 10.9 Hz, 1H), 2.03−1.93 (m, 1H), 1.91−1.71 (m, 2H), 1.57−1.45 (m, 1H) ppm. $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 176.1, 139.4, 128.5, 128.3, 126.9, 78.8, 65.1, 60.1, 59.7, 57.8, 52.2, 51.9, 26.2, 21.4 ppm. LCMS $(M + H)^+$: 276. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{16}H_{22}NO_3$ 276.1600; found 276.1615.

*2-Benzylhexahydropyrano[3,4-c]pyrrole-7a(1H)-carbonitrile (**27a**).* Protocol C was used. Two additional portions of **1** were added after 12 h (7.11 g, 0.03 mol, 0.3 equiv) and 24 h (7.11 g, 0.03 mol, 0.3 equiv). The residue was purified by column chromatography (hexane/EtOAc = 7:3). Yield: 19.60 g, 0.081 mol, 81%, yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ 7.42−7.18 (m, 5H), 3.89 (dt, J = 11.9, 3.9 Hz, 1H), 3.84−3.70 (m, 4H), 3.63 (td, J = 11.6, 2.7 Hz, 1H), 3.05 (d, J = 9.3 Hz, 1H), 3.02−2.92 (m, 1H), 2.96 (d, J = 9.3 Hz, 1H), 2.84 (t, J = 9.3 Hz, 1H), 2.52 (dd, J = 10.2, 6.5 Hz, 1H), 2.29−2.15 (m, 1H), 1.90 (d, J = 14.2 Hz, 1H) ppm. $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 138.7, 128.5, 128.5, 127.3, 122.8, 65.4, 64.3, 62.3, 59.7, 53.4, 41.6, 37.2, 30.6 ppm. LCMS $(M + H)^+$: 243. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{15}H_{19}N_2O$ 243.1497; found 243.1484.

*Methyl 2-Benzylhexahydropyrano[3,4-c]pyrrole-7a(1H)-carboxylate (**28a**).* Protocol C was used. Two additional portions of **1** were added after 12 h (7.11 g, 0.03 mol, 0.3 equiv) and 24 h (7.11 g, 0.03 mol, 0.3 equiv). The residue was purified by column chromatography (hexane/EtOAc = 8:2). Yield: 23.38 g, 0.085 mol, 85%, yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ 7.35−7.24 (m, 5H), 3.89−3.62 (m, 8H), 3.51 (td, J = 11.4, 2.8 Hz, 1H), 2.95 (d, J = 9.2 Hz, 1H), 2.91 (d, J = 7.9 Hz, 1H), 2.83 (d, J = 9.0 Hz, 1H), 2.79 (d, J = 9.0 Hz, 1H), 2.71−2.61 (m, 1H), 2.17−2.05 (m, 1H), 2.03−1.94 (m, 1H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 175.9, 139.4, 128.6, 128.4, 127.0, 66.4, 64.9, 62.4, 60.3, 54.9, 52.2, 48.6, 39.4, 30.3 ppm. LCMS $(M + H)^+$: 276. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{16}H_{22}NO_3$ 276.1600; found 276.1612.

*Methyl 2-Benzylhexahydropyrano[3,4-c]pyrrole-3a(4H)-carboxylate (**29a**).* Protocol C was used. Two additional portions of **1** were added after 12 h (7.11 g, 0.03 mol, 0.3 equiv) and 24 h (7.11 g, 0.03 mol, 0.3 equiv). The residue was purified by column chromatography (hexane/EtOAc = 7:3). Yield: 22.83 g, 0.083 mol, 83%, yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ 7.34−7.20 (m, 5H), 4.08 (d, J = 11.7 Hz, 1H), 3.77−3.74 (m, 1H), 3.73 (s, 3H), 3.72−3.60 (m, 4H), 2.98−2.83 (m, 3H), 2.79 (d, J = 7.1 Hz, 1H), 2.66 (d, J = 9.7 Hz, 1H), 2.02−1.90 (m, 1H), 1.59−1.49 (m, 1H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 175.2, 139.3, 128.6, 128.4, 127.1, 69.7, 64.7, 60.3, 59.2, 56.5, 52.4, 50.9, 36.3, 24.9 ppm. LCMS $(M + H)^+$: 276. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{16}H_{22}NO_3$ 276.1600; found 276.1608.

*Methyl 2-Benzyl-7a-fluorohexahydropyrano[3,4-c]pyrrole-3a-(4H)-carboxylate (**30a**).* Protocol C was used. Two additional portions of **1** were added after 12 h (7.11 g, 0.03 mol, 0.3 equiv) and 24 h (7.11 g, 0.03 mol, 0.3 equiv). The crude product was purified by column chromatography (gradient, hexane/EtOAc = 3:1 to 5:1). Yield: 19.92 g, 0.068 mol, 68%, yellow oil. R_f = 0.15. ^1H NMR (400 MHz, D_2O): δ 7.69−7.47 (m, 5H), 4.65−4.48 (m, 2H), 4.40−4.22 (m, 2H), 4.16 (br s, 1H), 4.12−3.88 (m, 2H), 3.82 (s, 3H), 3.65−3.39 (m, 3H), 2.58−2.40 (m, 1H), 2.16 (d, J = 13.7 Hz, 1H) ppm. $^{13}C\{^1H\}$ NMR (151 MHz, D_2O): δ 169.6 (d, J = 4.3 Hz), 130.7, 130.4, 129.4, 129.0, 98.8 (d, J = 186.9 Hz), 70.0 (br s), 64.7 (d, J = 10.4 Hz), 60.1 (br s), 58.2 (d, J = 25.1 Hz), 56.1, 53.9 (d, J = 18.7 Hz), 53.4, 27.1 (d, J = 21.0 Hz) ppm. $^{19}F\{^1H\}$ NMR (376 MHz, D_2O): δ −141.6 (s) ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{16}H_{21}FNO_3$ 294.1505; found 294.1521.

*Methyl-6-benzylhexahydropyrano[2,3-c]pyrrole-7a(2H)-carboxylate (**31a**).* Protocol D. The residue was purified by column chromatography (hexane/EtOAc = 7:3). Yield: 19.25 g, 0.07 mol, 70%, yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ 7.36−7.23 (m, 5H), 3.91 (d, J = 11.4 Hz, 1H), 3.78 (s, 3H), 3.77−3.69 (m, 2H), 3.54 (td, J = 11.5, 2.2 Hz, 1H), 3.23 (d, J = 11.1 Hz, 1H), 2.95−2.79 (m, 3H), 2.76 (d, J = 11.1 Hz, 1H), 1.91−1.64 (m, 3H), 1.37 (d, J = 12.2 Hz, 1H) ppm. $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 173.4, 139.2, 128.9, 128.4, 127.1, 83.7, 65.8, 65.1, 60.9, 55.7, 52.4, 39.3, 20.9, 20.7 ppm. LCMS $(M + H)^+$: 276. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{16}H_{22}NO_3$ 276.1600; found 276.1625.

*Methyl-2-benzyl-5-methyloctahydro-7aH-pyrrolo[3,4-c]pyridine-7a-carboxylate (**32a**).* Protocol C was used. An additional portion of **1** was added after 12 h (7.11 g, 0.03 mol, 0.3 equiv). The residue was purified by column chromatography (hexane/EtOAc = 9:1). Yield: 22.75 g, 0.079 mol, 79%, yellow oil. ^1H NMR (400 MHz, DMSO-d_6): δ 7.31−7.19 (m, 5H), 3.69 (d, J = 13.3 Hz, 1H), 3.62 (d, J = 13.2 Hz, 1H), 3.62 (s, 3H), 2.81 (d, J = 9.1 Hz, 1H), 2.78−2.56 (m, 4H), 2.44−2.31 (m, 2H), 2.17 (dd, J = 11.8, 4.4 Hz, 1H), 2.09 (s, 3H), 2.01−1.84 (m, 3H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6): δ 175.2, 139.4, 128.2, 128.1, 126.7, 61.2, 59.5, 55.3, 55.0, 52.2, 51.8, 48.1, 46.1, 30.0 ppm. LCMS $(M + H)^+$: 289. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{25}N_2O_2$ 289.1916; found 289.1934.

*Methyl-2-benzyl-5-tosyloctahydro-7aH-pyrrolo[3,4-c]pyridine-7a-carboxylate (**33a**).* Protocol C was used. An additional portion of **1** was added after 12 h (7.11 g, 0.03 mol, 0.3 equiv). The residue was purified by column chromatography (hexane/EtOAc = 9:1). Yield: 38.95 g, 0.091 mol, 91%, white solid. mp = 146−148 °C. ^1H NMR (600 MHz, DMSO-d_6): δ 7.71 (d, J = 8.6 Hz, 2H), 7.53 (d, J = 8.7 Hz, 2H), 7.49−7.25 (m, 2 5H), 3.71 (s, 2H), 3.64 (s, 3H), 3.46−3.44 (m, 1H), 3.29 (dd, J = 12.8, 3.8 Hz, 1H), 2.85 (d, J = 9.5 Hz, 1H), 2.83−2.71 (m, 2H), 2.68 (d, J = 9.5 Hz, 1H), 2.50 (s, 3H), 2.12−2.00 (m, 2H) ppm. $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6): δ 174.5, 143.4, 139.0, 133.1, 129.9, 128.2, 128.2, 127.3, 126.8, 61.5, 59.0, 54.7, 52.1, 48.0, 44.6, 42.7, 38.6, 29.1, 21.0 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{23}H_{29}N_2O_4S$ 429.1848; found 429.1845.

*Tert-butyl (2-benzyl-7a-(trifluoromethyl)octahydro-5H-pyrrolo-[3,4-c]pyridine-5-carboxylate (**34a**).* Protocol D was used. The residue was purified by column chromatography (hexane/EtOAc = 9:1). Yield: 24.19 g, 0.063 mol, 63%, yellow oil. Mixture of diastereomers (~3:2). ^1H NMR (400 MHz, $CDCl_3$): δ 7.34−7.27 (m, 5H), 3.67−3.31 (m, 6H), 2.89−2.68 (m, 2H), 2.62−2.45 (m, 3H), 2.12−2.02 (m, 1H), 1.90−1.76 (m, 1H), 1.50, 1.47 (2 × s, 9H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 155.8, 155.5, 138.8, 129.0 (q, J = 280.6 Hz), 128.5, 127.2, 59.6, 57.9, 57.4, 47.0, 41.7, 40.7, 39.4, 38.7, 38.3, 28.6, 26.1, 26.0 ppm. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$): δ −76.3, −76.4 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{20}H_{28}F_3N_2O_2$ 385.2103; found 385.2118.

*5-(Tert-butyl) 7a-methyl-2-benzyl-3a-fluorohexahydro-1H-pyrrolo[3,4-c]pyridine-5,7a-dicarboxylate (**35a**).* Protocol C was used. Two additional portions of **1** were added after 12 h (7.11 g, 0.03 mol, 0.3 equiv) and 24 h (7.11 g, 0.03 mol, 0.3 equiv). The crude product was purified by column chromatography (hexane/EtOAc, 8:1). R_f = 0.26. Yield: 20.78 g, 0.053 mol, 53%, yellow oil. Mixture of diastereomers (~3:2). ^1H NMR (500 MHz, $CDCl_3$): δ 7.43−7.23 (m, 5H), 4.31−3.95 (m, 2H), 3.94−3.75 (m, 2H), 3.73, 3.71 (2 × s, 3H), 3.69−3.62 (m, 1H), 3.47−3.12 (m, 4H), 2.89−2.68 (m, 2H), 2.19 (br s, 1H), 1.92−1.81 (m, 2H), 1.47, 1.42 (2 × s, 9H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 171.8, 171.8, 155.0, 154.6, 138.9, 128.4, 127.1, 100.2, 98.7, 80.2, 61.0, 60.8, 59.7, 59.7, 53.6, 53.4, 52.1, 45.6, 45.3, 44.5, 44.2, 40.5, 39.4, 31.8, 31.5, 28.5 ppm. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$): δ −146.1 (s), −146.4 (s) ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{21}H_{30}FN_2O_4$ 393.2190; found 393.2173.

*5-tert-Butyl 3a-Ethyl-2-benzylhexahydro-5H-pyrrolo[3,4-c]-pyridine-3a,5(4H)-dicarboxylate (**36a**).* Protocol D was used. The residue was purified by column chromatography (hexane/EtOAc = 8:2). Yield: 36.46 g, 0.093 mol, 93%, yellow oil. ^1H NMR (500 MHz, DMSO-d_6): δ 7.34−7.19 (m, 5H), 4.11−3.72 (m, 2H), 3.63−3.40 (m, 2H), 3.33−3.05 (m, 4H), 2.72−2.63 (m, 3H), 2.46−2.27 (m, 2H), 1.83−1.75 (m, 1H), 1.63−1.55 (m, 1H), 1.37 (s, 9H), 1.16 (br s, 3H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6): δ 174.3, 154.5, 153.8, 138.8, 128.2, 128.2, 126.8, 78.4, 60.5, 60.3, 58.7, 58.4, 58.2, 52.0, 45.2, 43.9, 40.9, 40.3, 36.7, 28.0, 24.5, 24.2, 13.9 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{22}H_{33}N_2O_4$ 389.2440; found 389.2426.

*tert-Butyl (2-Benzyl-3a-(trifluoromethyl)octahydro-5H-pyrrolo-[3,4-c]pyridine-5-carboxylate (**37a**).* Protocol D was used. The

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residue was purified by column chromatography (hexane/EtOAc = 8:2). Yield: 24.96 g, 0.065 mol, 65%, yellow oil. Mixture of diastereomers (~3:2). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.35−7.21 (m, 5H), 3.96, 3.87 (2 × d, J = 14.4 Hz, 1H), 3.65−3.07 (m, 4H), 2.70−2.44 (m, 3H), 2.44−2.32 (m, 1H), 1.95−1.68 (m, 2H), 1.58−1.33 (m, 11H) ppm. ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 155.8, 155.0, 138.9, 128.5, 128.5, 128.3 (d, J = 280.7 Hz), 127.2, 79.9, 79.7, 59.5, 58.9, 58.6, 42.8, 41.2, 40.8, 40.3, 36.0, 35.9, 28.6, 28.5, 24.9, 24.7 ppm. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{20}H_{28}F_3N_2O_2$ 385.2103; found 385.2129.

*6-Benzyl-4a-(trifluoromethyl)octahydrothiopyrano[2,3-c]pyrrole 1,1-Dioxide (**38a**).* Protocol A was used. Crude product was crystallized from a mixture of $CHCl_3$:hexane. Yield: 32.63 g, 0.098 mol, 98%, colorless crystals, mp = 102−104 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39−7.19 (m, 5H), 3.74 (d, J = 12.8 Hz, 1H), 3.54 (d, J = 12.2 Hz, 2H), 3.52−3.42 (m, 1H), 3.36−3.24 (m, 1H), 3.12−2.98 (m, 1H), 2.87 (d, J = 8.9 Hz, 1H), 2.82 (d, J = 10.1 Hz, 1H), 2.65 (d, J = 9.7 Hz, 1H), 2.46−2.33 (m, 1H), 2.31−2.11 (m, 2H), 1.95−1.85 (m, 1H) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 137.6, 128.7, 128.4 (d, J = 23.2 Hz), 127.7, 127.1 (q, J = 281.7 Hz), 61.2, 60.0, 58.9, 55.4, 52.5 (q, J = 26.0 Hz), 46.0, 23.5, 17.6 ppm. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ −75.62 (s), −75.65 (s), −162.20 (s), −162.23 (s) ppm. GCMS (M): 333. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{15}H_{19}F_3NO_2S$ 334.1089; found 334.1082.

*Methyl 2-Benzylhexahydrothiopyrano[3,4-c]pyrrole-7a(1H)-carboxylate 5,5-Dioxide (**39a**).* Protocol B was used. The residue was purified by column chromatography (hexane/EtOAc = 8:2). Yield: 26.49 g, 0.082 mol, 82%, brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37−7.26 (m, 5H), 3.77 (s, 3H), 3.68 (s, 2H), 3.28−2.98 (m, 6H), 2.89 (d, J = 9.7 Hz, 1H), 2.86−2.80 (m, 1H), 2.77 (d, J = 9.7 Hz, 1H), 2.54 (dd, J = 7.4, 5.1 Hz, 2H) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 174.6, 138.6, 128.5, 127.3, 62.5, 59.5, 56.8, 52.9, 50.4, 49.8, 49.2, 39.7, 29.5 ppm. LCMS (M + H)$^+$: 324. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{16}H_{22}NO_4S$ 324.1270; found 324.1262.

*6-Benzyl-7a-(trifluoromethyl)octahydrothiopyrano[2,3-c]pyrrole 1,1-Dioxide (**40a**).* Protocol A was used. Crude product was crystallized from CCl_4. Yield: 26.97 g, 0.081 mol, 81%, colorless crystals, mp = 68−69 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38−7.25 (m, 5H), 3.79 (s, 2H), 3.45 (d, J = 12.6 Hz, 1H), 3.34 (d, J = 12.5 Hz, 1H), 3.30−3.17 (m, 3H), 3.11−2.99 (m, 1H), 2.99−2.89 (m, 1H), 2.33 (br s, 1H), 2.11−1.95 (m, 1H), 1.95−1.79 (m, 2H) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 138.7, 128.6, 128.5, 127.3, 124.6 (q, J = 281.6 Hz), 71.8 (q, J = 25.8 Hz), 59.1, 55.7, 52.8, 50.7, 41.5, 21.0, 20.2 ppm. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ −67.6 (s) ppm. GCMS (M): 333. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{15}H_{19}F_3NO_2S$ 334.1089; found 334.1082.

*2-Benzyloctahydrocyclohepta[c]pyrrole-3a(1H)-carbonitrile (**41a**).* Protocol C was used. Two additional portions of **1** were added after 12 h (7.11 g, 0.03 mol, 0.3 equiv) and 24 h (7.11 g, 0.03 mol, 0.3 equiv). The residue was purified by column chromatography (hexane/EtOAc = 7:3). Yield: 12.45 g, 0.049 mol, 49%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39−7.24 (m, 5H), 3.62 (d, J = 13.1 Hz, 1H), 3.53 (d, J = 13.1 Hz, 1H), 3.26 (d, J = 9.5 Hz, 1H), 3.18 (t, J = 8.4 Hz, 1H), 2.76−2.61 (m, 1H), 2.16 (d, J = 9.5 Hz, 1H), 1.99−1.82 (m, 5H), 1.78−1.56 (m, 3H), 1.46−1.13 (m, 3H) ppm. ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 138.4, 128.6, 128.4, 127.2, 126.7, 66.2, 61.6, 59.2, 49.2, 45.7, 33.5, 31.2, 30.7, 28.6, 26.3 ppm. LCMS (M + H)$^+$: 255. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{17}H_{23}N_2$ 255.1861; found 255.1852.

General Procedure E for Synthesis of 2b, 6b, 7b, 9b−12b, 24b−26b, 28b−32b, 39b, and 41b. See **2b** as an example. Scale: 0.1 mol for all derivatives.

*3-(tert-Butoxycarbonyl)-3-azabicyclo[3.2.0]heptane-1-carboxylic Acid (**2b**).* A solution of **2a** (24.50 g, 0.1 mol, 1.0 equiv) in MeOH (500 mL) was hydrogenated in the presence of 10% Pd/C (5.00 g) at a pressure of 50 atm for 15 h at rt. Then the catalyst was filtered off, and the residue was washed with MeOH. The filtrate was concentrated to a half of original volume, filtered through a thin pad of silica gel, and concentrated to dryness. The residue was dissolved in CH_2Cl_2 (250 mL) and Et_3N (10.10 g, 0.1 mol, 1.0 equiv) was added to the mixture. Then Boc_2O (21.80 g, 0.1 mol, 1.0 equiv) in CH_2Cl_2 (25 mL) was added dropwise at rt (the mixture can be cooled in a water bath). The solution was stirred overnight at rt. The mixture was washed with 0.5 M HCl (1 × 20 mL), water (1 × 20 mL), and brine (1 × 20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was dissolved in MeOH (200 mL), and NaOH (8.00 g, 0.2 mol, 2.0 equiv) was added to the mixture. The solution was stirred at rt overnight. The solution was concentrated under reduced pressure. The residue was washed with methyl *tert*-butyl ether (2 × 50 mL) and then acidified with 1 M HCl to pH ~ 4. The solution was extracted with EtOAc (3 × 100 mL). The combined fractions were washed with brine (1 × 100 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Yield: 19.00 g, 0.079 mol, 79%, white solid, mp = 104−105 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.54 (s, 1H), 3.59 (d, J = 11.2 Hz, 1H), 3.44 (d, J = 11.3 Hz, 2H), 3.27−3.16 (m, 1H), 3.02−2.94 (m, 1H), 2.47−2.36 (m, 1H), 2.17−2.06 (m, 1H), 1.90−1.79 (m, 1H), 1.64−1.53 (m, 1H), 1.42 (s, 9H) ppm. ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 175.4, 154.1, 78.7, 54.4, 52.3, 42.1, 41.0, 28.1, 26.7, 21.3 ppm. LCMS (M − H)$^-$: 240. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{12}H_{20}NO_4$ 242.1392; found 242.1381.

*2-(tert-Butoxycarbonyl)hexahydrocyclopenta[c]pyrrole-3a(1H)-carboxylic Acid (**6b**).* General procedure E. Yield: 19.60 g, 0.077 mol, 77%, white solid, mp = 95−97 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.46 (s, 1H), 3.76 (d, J = 11.4 Hz, 1H), 3.48 (dd, J = 11.0, 8.2 Hz, 1H), 3.16 (d, J = 11.4 Hz, 1H), 3.07 (dd, J = 11.1, 4.1 Hz, 1H), 2.78 (br s, 1H), 2.10−1.99 (m, 1H), 1.94−1.78 (m, 1H), 1.76−1.59 (m, 3H), 1.49−1.42 (m, 1H), 1.39 (s, 9H) ppm. ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6): δ 177.0, 153.3, 78.4, 59.3, 58.4, 54.3, 51.5, 47.7, 46.8, 35.8, 32.1, 28.1, 25.0 ppm. LCMS (M − H)$^-$: 254. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{13}H_{22}NO_4$ 256.1549; found 256.1542.

*2-(tert-Butoxycarbonyl)-6a-fluorohexahydrocyclopenta[c]-pyrrole-3a(1H)-carboxylic Acid (**7b**).* General procedure E. Yield: 23.80 g, 0.087 mol, 87%, white solid, mp = 126−127 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.07 (d, J = 11.5 Hz, 1H), 3.90−3.65 (m, 2H), 3.41 (d, J = 11.2 Hz, 1H), 2.59−2.46 (m, 1H), 2.40−2.25 (m, 1H), 2.10−1.93 (m, 2H), 1.90−1.68 (m, 2H), 1.46 (s, 9H) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 177.0 (d, J = 3.6 Hz), 154.5, 110.3 (d, J = 203.2 Hz), 109.7 (d, J = 200.7 Hz), 80.5, 61.0, 60.3, 55.4 (d, J = 30.7 Hz), 53.7, 36.1 (d, J = 22.1 Hz), 35.6 (d, J = 24.7 Hz), 34.2, 28.6, 22.7, 22.5 ppm. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ −154.9 (s), −155.4 (s) ppm. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{13}H_{21}FNO_4$ 274.1455; found 274.1451.

*5-(tert-Butoxycarbonyl)hexahydro-3aH-furo[2,3-c]pyrrole-3a-carboxylic Acid (**9b**).* General procedure E. Cleavage of *N*-Bn bond was performed under modified conditions: 10 atm (H_2), 10% Pd/C, 50 °C, MeOH, 15h. Yield: 20.56 g, 0.08 mol, 80%, white solid, mp = 109−110 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.22 (br s, 1H), 4.61 (d, J = 4.5 Hz, 1H), 4.07 (dd, J = 15.2, 7.0 Hz, 1H), 4.00−3.90 (m, 2H), 3.66 (d, J = 12.3 Hz, 1H), 3.59−3.34 (m, 2H), 2.61−2.47 (m, 1H), 2.16−1.99 (m, 1H), 1.44 (s, 9H) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 178.0, 154.6, 86.6, 86.0, 80.4, 68.9, 59.8, 58.9, 53.9, 52.4, 51.8, 36.5, 28.5 ppm. LCMS (M − H)$^-$: 256. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{12}H_{20}NO_5$ 258.1341; found 258.1348.

*5-(tert-Butoxycarbonyl)tetrahydro-1H-furo[3,4-c]pyrrole-3a(3H)-carboxylic Acid (**10b**).* General procedure E. Yield: 17.48 g, 0.068 mol, 68%, white solid, mp = 98−99 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.82 (br s, 1H), 4.22 (d, J = 9.2 Hz, 1H), 4.09 (t, J = 7.9 Hz, 1H), 3.91 (d, J = 11.6 Hz, 1H), 3.79 (d, J = 9.2 Hz, 1H), 3.72−3.60 (m, 2H), 3.54 (br s, 1H), 3.38 (br s, 1H), 3.24−3.06 (m, 1H), 1.45 (s, 9H) ppm. ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 178.1, 154.5, 80.5, 76.0, 74.3, 60.0 (br s), 53.1, 50.5 (br s), 48.1 (br s), 28.6 ppm. LCMS (M − H)$^-$: 256. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{12}H_{20}NO_5$ 258.1341; found 258.1329.

*5-(tert-Butoxycarbonyl)-3,3-dimethyltetrahydro-1H-furo[3,4-c]-pyrrole-3a(3H)-carboxylic Acid (**11b**).* General procedure E. Yield: 22.23 g, 0.078 mol, 78%, white solid, mp = 138−140 °C. ^{1}H NMR

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(400 MHz, $CDCl_3$): δ 10.99 (br s, 1H), 4.18 (t, J = 9.2 Hz, 1H), 3.85 (br s, 1H), 3.67−3.55 (m, 3H), 3.49−3.41 (m, 1H), 3.41 (br s, 1H), 1.45 (s, 9H), 1.39 (s, 3H), 1.24 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 177.1, 154.6, 83.1, 80.3, 70.7, 66.4 (br s), 65.4 (br s), 50.8, 45.3 (br s), 44.6 (br s), 28.6, 24.5, 23.1 ppm. LCMS (M − H)$^-$: 284. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{14}H_{24}NO_5$ 286.1654; found 286.1645.

*5-(tert-Butoxycarbonyl)hexahydro-6aH-furo[2,3-c]pyrrole-6a-carboxylic Acid (**12b**).* General procedure E. Yield: 21.59 g, 0.084 mol, 84%, white solid, mp = 108−109 °C. ^1H NMR (400 MHz, DMSO-d_6): δ 12.99 (br s, 1H), 3.98 (dd, J = 14.8, 7.2 Hz, 1H), 3.93−3.82 (m, 1H), 3.64 (d, J = 11.8 Hz, 1H), 3.60−3.52 (m, 1H), 3.49 (d, J = 12.1 Hz, 1H), 3.17 (dd, J = 11.1, 5.6 Hz, 1H), 2.99 (br s, 1H), 2.16−2.01 (m, 1H), 1.82−1.70 (m, 1H), 1.39 (s, 9H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6): δ 173.2, 153.3, 78.7, 68.7, 54.5, 50.9, 47.5, 46.5, 31.1, 28.1 ppm. LCMS (M − H)$^-$: 256. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{12}H_{20}NO_5$ 258.1341; found 258.1328.

*5-(tert-Butoxycarbonyl)tetrahydro-1H-thieno[3,4-c]pyrrole-3a-(3H)-carboxylic Acid 2,2-Dioxide (**23b**).* General procedure E. Yield: 21.66 g, 0.071 mol, 71%, white solid, mp = 162−163 °C. ^1H NMR (400 MHz, DMSO-d_6): δ 13.37 (br s, 1H), 3.87 (d, J = 11.8 Hz, 1H), 3.72 (dd, J = 12.7, 9.3 Hz, 1H), 3.59 (d, J = 14.2 Hz, 1H), 3.46 (d, J = 11.9 Hz, 1H), 3.45−3.40 (m, 2H), 3.39 (d, J = 14.3 Hz, 1H), 3.27 (br s, 2H), 3.23−3.16 (m, 1H), 1.39 (s, 9H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6): δ 173.5, 153.1, 79.0, 55.6, 53.8, 53.6, 49.6, 41.7, 40.8, 28.1 ppm. LCMS (M − H)$^-$: 304. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{12}H_{20}NO_6S$ 306.1011; found 306.1002.

*2-(tert-Butoxycarbonyl)octahydro-3aH-isoindole-3a-carboxylic Acid (**24b**).* General procedure E. Yield: 19.10 g, 0.071 mol, 71%, white solid, mp = 133−134 °C. ^1H NMR (400 MHz, DMSO-d_6): δ 12.60 (s, 1H), 3.41 (dd, J = 14.5, 10.7 Hz, 1H), 3.35−3.23 (m, 1H), 3.21 (d, J = 10.8 Hz, 1H), 3.16−3.03 (m, 1H), 1.85−1.76 (m, 1H), 1.69−1.57 (m, 1H), 1.53−1.41 (m, 3H), 1.39 (s, 9H), 1.36−1.29 (m, 4H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6): δ 176.0, 153.8, 78.4, 53.0, 52.8, 50.1, 49.3, 48.8, 48.5, 38.3, 37.5, 28.6, 28.5, 28.1, 24.3, 21.9, 21.3 ppm. LCMS (M − H)$^-$: 268. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{14}H_{24}NO_4$ 270.1705; found 270.1717.

*2-(tert-Butoxycarbonyl)-6,6-difluorooctahydro-3aH-isoindole-3a-carboxylic Acid (**25b**).* General procedure E. Yield: 22.57 g, 0.074 mol, 74%, white solid, mp = 157−158 °C. Mixture of diastereomers (∼1:1). ^1H NMR (400 MHz, DMSO-d_6): δ 12.97 (br s, 1H), 3.55 (t, J = 11.5 Hz, 1H), 3.40−3.30 (m, 2H), 3.17−3.08 (m, 1H), 2.82−2.68 (m, 1H), 2.17−1.94 (m, 3H), 1.92−1.74 (m, 3H), 1.39, 1.39 (2 × s, 9H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6): δ 175.3, 153.7, 153.6, 123.6 (t, J = 239.7 Hz), 78.59, 78.57, 51.0, 50.9, 49.4, 49.2, 48.9, 48.5, 38.1, 37.3, 32.3 (t, J = 23.7 Hz), 29.3 (t, J = 24.3 Hz), 28.1, 25.54, 25.49 ppm. $^{19}F\{^1H\}$ NMR (376 MHz, DMSO-d_6): δ −90.4 (s), −91.0 (s) ppm. LCMS (M − H)$^-$: 304. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{14}H_{22}F_2NO_4$ 306.1517; found 306.1510.

*6-(tert-Butoxycarbonyl)hexahydropyrano[2,3-c]pyrrole-4a(2H)-carboxylic Acid (**26b**).* General procedure E. Cleavage of *N*-Bn bond was performed under modified conditions: 10 atm (H_2), 10% Pd/C, 50 °C, MeOH, 15h. Yield: 18.16 g, 0.067 mol, 67%, beige solid, mp = 142−143 °C. ^1H NMR (400 MHz, DMSO-d_6): δ 12.81 (br s, 1H), 4.15−4.03 (m, 1H), 3.83, 3.80 (2 × d, J = 2.5 Hz, 1H), 3.66 (t, J = 10.2 Hz, 1H), 3.42−3.24 (m, 3H), 3.20, 3.17 (2 × d, J = 5.2 Hz, 1H), 1.90−1.80 (m, 2H), 1.73−1.59 (m, 1H), 1.51−1.43 (m, 1H), 1.39, 1.38 (2 × s, 9H) ppm. $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6): δ 175.6, 153.7, 153.9, 78.5, 78.48, 77.7, 76.9, 65.5, 52.1, 51.8, 50.9, 50.0, 48.1, 47.9, 28.2, 28.1, 25.3, 20.4 ppm. LCMS (M + H)$^+$: 272. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{13}H_{22}NO_5$ 272.1498; found 272.1477.

*2-(tert-Butoxycarbonyl)hexahydropyrano[3,4-c]pyrrole-7a(1H)-carboxylic Acid (**28b**).* General procedure E. Yield: 18.70 g, 0.069 mol, 69%, white solid, mp = 148−149 °C. ^1H NMR (400 MHz, DMSO-d_6): δ 12.86 (s, 1H), 3.70−3.58 (m, 2H), 3.54−3.26 (m, 6H), 3.25−3.13 (m, 1H), 1.91−1.82 (m, 1H), 1.64−1.51 (m, 1H), 1.39 (s, 9H) ppm. $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6): δ 175.6, 154.3, 154.2, 79.02, 78.97, 65.0, 64.9, 64.32, 64.27, 54.0, 53.9, 48.0, 47.1, 47.05, 46.8, 39.0, 38.1, 28.9, 28.8, 28.6 ppm. LCMS (M + H)$^+$: 272. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{13}H_{22}NO_5$ 272.1498; found 272.1491.

*2-(tert-Butoxycarbonyl)hexahydropyrano[3,4-c]pyrrole-3a(4H)-carboxylic Acid (**29b**).* General procedure E. Yield: 19.24 g, 0.071 mol, 71%, white solid, mp = 127−128 °C. ^1H NMR (400 MHz, DMSO-d_6): δ 12.86 (s, 1H), 3.80, 3.77 (2 × d, J = 5.9 Hz, 1H), 3.70−3.61 (m, 1H), 3.53−3.33 (m, 4H), 3.26−3.17 (m, 2H), 2.71−2.57 (m, 1H), 1.83−1.71 (m, 1H), 1.39 (s, 9H), 1.38−1.27 (m, 1H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6): δ 174.4, 153.8, 153.7, 78.6, 67.39, 67.35, 64.3, 64.2, 50.0, 49.6, 49.5, 49.03, 48.98, 48.7, 35.9, 35.2, 28.1, 24.54, 24.48 ppm. LCMS (M − H)$^-$: 270. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{13}H_{22}NO_5$ 272.1498; found 272.1484.

*2-(tert-Butoxycarbonyl)-7a-fluorohexahydropyrano[3,4-c]-pyrrole-3a(4H)-carboxylic Acid (**30b**).* General procedure E. Yield: 21.10 g, 0.073 mol, 73%, white solid, mp = 167−169 °C. ^1H NMR (400 MHz, DMSO-d_6): δ 12.93 (s, 1H), 4.02−3.91 (m, 2H), 3.88, 3.79 (2 × d, J = 13.4 Hz, 1H), 3.69−3.43 (m, 3H), 3.27−3.16 (m, 2H), 2.45−2.29 (m, 1H), 1.95−1.83 (m, 1H), 1.41 (s, 9H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6): δ 170.88, 170.86, 153.5, 99.2 (d, J = 186.3 Hz), 98.4 (d, J = 185.6 Hz), 79.1, 70.2 (d, J = 4.7 Hz), 64.9 (d, J = 9.8 Hz), 53.4, 53.3, 53.2, 53.1, 52.9, 52.6, 52.5, 49.3, 49.1, 28.4, 28.2, 28.1 ppm. $^{19}F\{^1H\}$ NMR (376 MHz, DMSO-d_6): δ −142.76 (s) ppm. LCMS (M − H)$^-$: 288. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{13}H_{21}FNO_5$ 290.1404; found 290.1384.

*6-(tert-Butoxycarbonyl)hexahydropyrano[2,3-c]pyrrole-7a(2H)-carboxylic Acid (**31b**).* General procedure E. Cleavage of the *N*-Bn bond was performed under modified conditions: 10 atm (H_2), 10% Pd/C, 50 °C, MeOH, 15h. Yield: 20.33 g, 0.075 mol, 75%, white solid, mp = 157−158 °C. Mixture of diastereomers (∼1:1). ^1H NMR (400 MHz, DMSO-d_6): δ 13.16 (br s, 1H), 3.79−3.70 (m, 1H), 3.55−3.24 (m, 5H), 2.79−2.63 (m, 1H), 1.65 (br s, 3H), 1.40, 1.38 (2 × s, 9H), 1.33−1.25 (m, 1H) ppm. $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6): δ 172.0, 171.9, 153.5, 153.3, 82.0, 81.3, 78.62, 78.56, 64.1, 64.0, 57.1, 56.9, 46.7, 46.5, 37.7, 36.8, 28.13, 28.09, 19.52, 19.49, 19.0 ppm. LCMS (M − H)$^-$: 270. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{13}H_{22}NO_5$ 272.1498; found 272.1486.

*2-(tert-Butoxycarbonyl)-5-methyloctahydro-7aH-pyrrolo[3,4-c]-pyridine-7a-carboxylic Acid (**32b**).* General procedure E. Yield: 17.89 g, 0.063 mol, 63%, white solid, mp = 224−225 °C. Mixture of diastereomers (∼1:1). ^1H NMR (400 MHz, D_2O): δ 3.98−3.61 (m, 1H), 3.51−3.26 (m, 5H), 3.15−2.92 (m, 2H), 2.85 (s, 3H), 2.29 (d, J = 15.5 Hz, 1H), 2.18−2.02 (m, 1H), 1.82 (t, J = 13.4 Hz, 1H), 1.43 (s, 9H) ppm. $^{13}C\{^1H\}$ NMR (151 MHz, D_2O): δ 180.5, 178.6, 156.3, 81.8, 55.2, 54.6, 53.4, 51.8, 51.2, 50.3, 48.4, 47.9, 46.3, 45.8, 43.2, 37.7, 37.3, 27.6, 26.6, 26.1 ppm. LCMS (M − H)$^-$: 283. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{14}H_{25}N_2O_4$ 285.1814; found 285.1810.

*2-(tert-Butoxycarbonyl)hexahydrothiopyrano[3,4-c]pyrrole-7a-(1H)-carboxylic Acid 5,5-Dioxide (**39b**).* General procedure E. Yield: 24.88 g, 0.078 mol, 78%, white solid, mp = 78−79 °C. ^1H NMR (400 MHz, DMSO-d_6): δ 13.21 (br s, 1H), 3.63−3.51 (m, 1H), 3.50−3.36 (m, 3H), 3.31−3.01 (m, 5H), 2.40−2.28 (m, 1H), 2.25−2.09 (m, 1H), 1.40 (s, 9H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6): δ 174.61, 174.55, 153.6, 153.5, 78.7, 51.0, 50.9, 48.7, 48.2, 48.1, 48.0, 47.9, 47.8, 46.2, 46.1, 28.1, 27.3 ppm. LCMS (M − H)$^-$: 318. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{13}H_{22}NO_6S$ 320.1168; found 320.1175.

*2-(tert-Butoxycarbonyl)octahydrocyclohepta[c]pyrrole-3a(1H)-carboxylic Acid (**41b**).* Compound **41a** (25.40 g, 0.1 mol, 1.0 equiv) was dissolved in MeOH (200 mL), and NaOH (8.00 g, 0.2 mol, 2.0 equiv) was added to the mixture. The solution was stirred at reflux in an oil bath with a thermocouple overnight. The solution was concentrated under reduced pressure. The residue was washed with methyl *tert*-butyl ether (2 × 50 mL) and then acidified with 1 M HCl to pH ∼ 4. The solution was extracted with EtOAc (3 × 100 mL). The combined fractions were washed with brine (1 × 100 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was dissolved in MeOH (500 mL) and hydrogenated in the presence of 10% Pd/C (3.00 g) at pressure 50 atm for 15 h at

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rt. Then the catalyst was filtered off, and the residue was washed with MeOH. The filtrate was concentrated to a half of original volume, filtered through a thin pad of silica gel, and concentrated to dryness. The residue was dissolved in CH_2Cl_2 (250 mL), and Et_3N (10.10 g, 0.1 mol, 1.0 equiv) was added to the mixture. Then Boc_2O (21.80 g, 0.1 mol, 1.0 equiv) in CH_2Cl_2 (25 mL) was added dropwise at rt (the mixture can be cooled in a water bath). The solution was stirred overnight at rt. The mixture was washed with 0.5 M HCl (1 × 20 mL), water (1 × 20 mL), and brine (1 × 20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Yield: 17.26 g, 0.061 mol, 61%, white solid, mp = 97−98 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.55 (s, 1H), 3.79 (d, J = 11.1 Hz, 1H), 3.50 (br s, 1H), 3.03 (d, J = 10.9 Hz, 1H), 2.94 (dd, J = 11.1, 3.6 Hz, 1H), 2.69 (br s, 1H), 2.03 (br s, 1H), 1.77 (d, J = 11.8 Hz, 1H), 1.71 (d, J = 12.1 Hz, 1H), 1.67−1.42 (m, 4H), 1.37 (s, 9H), 1.31−1.16 (m, 3H) ppm. ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6): δ 177.4, 153.1, 78.3, 56.0, 55.2 (br s), 53.1 (br s), 43.6, 42.8, 33.3, 30.8, 30.2, 28.5, 28.1, 24.2 ppm. LCMS (M − H)$^-$: 282. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{15}H_{26}NO_4$ 284.1862; found 284.1845.

General Procedure F for synthesis of 3c−5c, 16c−21c, 34c, 35c, 38c, and 40c. See compound **3c** as an example. Scale: 0.10 mol for all derivatives. Note: Amines **4c**, **5c**, **17c**, **35c**, and **40c** were treated with 1 M HCl in dioxane, and the precipitate was filtered off to obtain amines hydrochlorides.

*1-(Trifluoromethyl)-6-thia-3-azabicyclo[3.2.0]heptane 6,6-Dioxide (**3c**).* A solution of **3a** (30.50 g, 0.10 mol, 1.0 equiv) in MeOH (300 mL) was hydrogenated in the presence of 10% Pd/C (3.00 g) at pressure 50 atm for 15 h at rt. Then the catalyst was filtered off, and the residue was washed with MeOH. The filtrate was concentrated to half the original volume, filtered through a thin pad of silica gel, and concentrated to dryness. The final product was crystallized from dioxane. Yield: 18.92 g, 0.088 mol, 88%, white solid, mp = 113−114 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.77 (d, J = 5.5 Hz, 1H), 4.51 (dd, J = 14.3, 2.3 Hz, 1H), 3.93 (d, J = 14.3 Hz, 1H), 3.83 (d, J = 13.5 Hz, 1H), 3.31 (d, J = 12.1 Hz, 1H), 3.18 (d, J = 12.6 Hz, 1H), 3.13 (dd, J = 13.8, 6.8 Hz, 1H), 2.45 (br s, 1H) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 125.9 (q, J = 278.3 Hz), 84.2, 70.1, 54.1, 50.1, 43.7 (q, J = 30.1 Hz) ppm. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6) δ −71.0 (s) ppm. LCMS (M + H)$^+$: 216. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_6H_9F_3NO_2S$ 216.0306; found 216.0300.

*1-Phenyl-6-thia-3-azabicyclo[3.2.0]heptane 6,6-dioxide Hydrochloride (**4c**).* General procedure F. Yield: 23.61 g, 0.091 mol, 91%, beige solid, mp = 154−155 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.52 (br s, 2H), 7.55 (d, J = 7.3 Hz, 2H), 7.45 (t, J = 7.5 Hz, 2H), 7.37 (t, J = 7.3 Hz, 1H), 5.31 (d, J = 8.5 Hz, 1H), 4.99 (d, J = 14.7 Hz, 1H), 4.61 (dd, J = 14.7, 3.5 Hz, 1H), 4.08−3.97 (m, 2H), 3.91 (dd, J = 13.8, 8.6 Hz, 1H), 3.23 (d, J = 12.0 Hz, 1H) ppm. ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6): δ 138.9, 128.9, 127.9, 126.6, 82.3, 73.3, 55.8, 46.6, 42.4 ppm. LCMS (M + H)$^+$: 224. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{11}H_{14}NO_2S$ 224.0745; found 224.0722.

*1-(4-Fluorophenyl)-6-thia-3-azabicyclo[3.2.0]heptane 6,6-dioxide Hydrochloride (**5c**).* General procedure F. Yield: 23.03 g, 0.083 mol, 83%, white solid, mp = 207−209 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.33 (br s, 2H), 7.61 (dd, J = 8.2, 5.4 Hz, 2H), 7.29 (t, J = 8.6 Hz, 2H), 5.30 (d, J = 8.5 Hz, 1H), 4.91 (d, J = 14.8 Hz, 1H), 4.61 (dd, J = 14.7, 3.3 Hz, 1H), 4.07−3.95 (m, 2H), 3.90 (dd, J = 13.7, 8.7 Hz, 1H), 3.24 (d, J = 11.9 Hz, 1H) ppm. ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6): δ 161.6 (d, J = 245.1 Hz), 135.1 (d, J = 2.9 Hz), 129.0 (d, J = 8.4 Hz), 115.6 (d, J = 21.5 Hz), 82.4, 73.4, 55.7, 46.6, 42.0 ppm. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6): δ −115.0 (s) ppm. LCMS (M + H)$^+$: 242. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{11}H_{13}FNO_2S$ 242.0651; found 242.0634.

*2-tert-Butyl 3a-Ethyl Tetrahydropyrrolo[3,4-c]pyrrole-2,3a-(1H,3H)-dicarboxylate (**16c**).* General procedure F. Yield: 21.02 g, 0.074 mol, 74%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.16 (dd, J = 14.1, 7.1 Hz, 2H), 3.79 (d, J = 11.7 Hz, 1H), 3.60−3.43 (m, 2H), 3.41 (d, J = 12.0 Hz, 1H), 3.30 (dd, J = 11.6, 7.6 Hz, 2H), 3.01−2.91 (m, 1H), 2.85 (d, J = 11.9 Hz, 1H), 2.70 (dd, J = 11.5, 5.1 Hz, 1H), 2.35 (br s, 1H), 1.44 (s, 9H), 1.26 (t, J = 7.1 Hz, 3H) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 174.9, 154.5, 79.9, 61.4, 58.4, 54.9, 53.4, 51.0 (br s), 49.6 (br s), 28.6, 14.3 ppm. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{14}H_{25}N_2O_4$ 285.1814; found 285.1802.

*tert-Butyl 3a-(Trifluoromethyl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate Hydrochloride (**17c**).* General procedure F. Cleavage of *N*-Bn bond was performed under modified conditions: 10 atm (H_2), 10% Pd/C, 50 °C, MeOH, 15h. Yield: 26.90 g, 0.085 mol, 85%, white solid, mp = 115−116 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.22 (br s, 2H), 3.80−3.53 (m,, 4H), 3.49−3.36 (m, 3H), 3.27−3.12 (m, 2H), 1.40 (s, 9H) ppm. ^{13}C{^{1}H} NMR (126 MHz, DMSO d_6): δ 152.9, 127.0 (q, J = 280 Hz), 79.4, 57.5 (br s), 50.2, 49.0, 48.6, 43.5, 28.0 ppm. ^{19}F{^{1}H} NMR (470 MHz, DMSO-d_6): δ −73.3 (s) ppm. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{12}H_{20}F_3N_2O_2$ 281.1477; found 281.1459.

*3a,6a-Bis(trifluoromethyl)octahydropyrrolo[3,4-c]pyrrole (**18c**).* General procedure F. Yield: 16.84 g, 0.068 mol, 68%, white solid, mp = 160−161 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.45 (d, J = 12.1 Hz, 4H), 2.99 (d, J = 12.0 Hz, 4H), 2.27 (br s, 2H) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 126.9 (q, J = 282.1 Hz), 64.0 (q, J = 23.4 Hz), 56.7 ppm. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ −67.5 (s) ppm. GCMS (M): 248. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_8H_{11}F_6N_2$ 249.0826; found 249.0835.

*1-tert-Butyl 6a-Methyl Hexahydropyrrolo[3,4-b]pyrrole-1,6a-dicarboxylate (**19c**).* General procedure F. Yield: 20.79 g, 0.077 mol, 77%, yellow oil. Mixture of diastereomers (∼1:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.71, 3.71 (2 × s, 3H), 3.70−3.51 (m, 3H), 3.28−3.01 (m, 2H), 2.86−2.66 (m, 2H), 2.56 (br s, 1H), 2.18−1.97 (m, 1H), 1.75−1.58 (m, 1H), 1.43, 1.38 (2 × s, 9H) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 174.5, 174.1, 154.4, 153.5, 80.3, 80.1, 76.7, 76.4, 58.2, 57.1, 54.1, 53.6, 52.7, 52.4, 48.5, 48.2, 29.2, 28.5, 28.4, 28.2 ppm. LCMS (M + H)$^+$: 271. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{13}H_{23}N_2O_4$ 271.1658; found 271.1666.

*3a-(Trifluoromethyl)hexahydro-2H-thieno[2,3-c]pyrrole 1,1-Dioxide (**20c**).* General procedure F. The final product was crystallized from a mixture of *i*-PrOH/benzene. Yield: 21.53 g, 0.094 mol, 94%, white solid, mp = 126−127 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.58 (dd, J = 7.2, 2.6 Hz, 1H), 3.40−3.25 (m, 3H), 3.14−3.05 (m, 3H), 2.82 (br s, 1H), 2.37−2.18 (m, 2H) ppm. ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 127.6 (q, J = 280.2 Hz), 64.1, 57.3 (q, J = 25.3 Hz), 55.2, 50.4, 49.2, 26.0 ppm. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6): δ −73.2 (s) ppm. LCMS (M + H)$^+$: 230. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_7H_{11}F_3NO_2S$ 230.0463; found 230.0451.

*6a-(Trifluoromethyl)hexahydro-2H-thieno[2,3-c]pyrrole 1,1-Dioxide (**21c**).* General procedure F. Crystallization from a mixture of benzene/hexane gave the pure product. Yield: 17.86 g, 0.078 mol, 78%, white solid, mp = 150−151 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.57 (d, J = 13.3 Hz, 1H), 3.54−3.43 (m, 1H), 3.26−3.08 (m, 2H), 3.03 (d, J = 13.3 Hz, 1H), 2.90−2.78 (m, 3H), 2.32−2.19 (m, 1H), 1.81−1.68 (m, 1H) ppm. ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 125.0 (q, J = 280.0 Hz), 73.7 (q, J = 24.8 Hz), 53.3, 51.2, 50.5, 47.3, 23.2 ppm. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6): δ −67.1 (s) ppm. GCMS (M): 229. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_7H_{11}F_3NO_2S$ 230.0463; found 230.0448.

*tert-Butyl 7a-(Trifluoromethyl)octahydro-5H-pyrrolo[3,4-c]-pyridine-5-carboxylate (**34c**).* General procedure F. Cleavage of *N*-Bn bond was performed under modified conditions: 10 atm (H_2), 10% Pd/C, 50 °C, MeOH, 15h. Yield: 23.52 g, 0.080 mol, 80%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.66 (br s, 1H), 3.42 (br s, 2H), 3.36−3.15 (m, 3H), 2.79 (d, J = 12.6 Hz, 1H), 2.65 (br s, 1H), 2.43 (br s, 1H), 2.08−2.00 (m, 2H), 1.70 (br s, 1H), 1.44 (s, 9H) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 155.6, 129.4 (q, J = 281 Hz), 80.0, 53.6, 51.2, 48.5, 40.9, 40.5, 39.5, 39.0, 38.5, 28.6, 28.5 (m), 25.1 ppm. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ −76.4 (s), −76.7 (s) ppm. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{13}H_{22}F_3N_2O_2$ 295.1633; found 295.1615.

*5-tert-Butyl 7a-methyl-3a-fluorohexahydro-1H-pyrrolo[3,4-c]-pyridine-5,7a-dicarboxylate Hydrochloride (**35c**).* General procedure F. Yield: 27.42 g, 0.081 mol, 81%, white solid, mp = 177−178 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.35 (br s, 2H), 4.28−4.10 (m, 1H), 3.96−3.79 (m, 1H), 3.73 (s, 3H), 3.72−3.68 (m, 1H), 3.48−3.30 (m, 3H), 3.13 (br s, 1H), 2.08−1.88 (m, 2H), 1.42 (s, 9H)

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ppm. $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6): δ 169.0 (d, J = 3.8 Hz), 153.8, 98.5 (d, J = 186.8 Hz), 80.0, 52.7 (d, J = 18.9 Hz), 52.7, 50.4, 49.9 (d, J = 25.5 Hz), 42.2 (br s), 30.2, 27.9 ppm. LCMS (M + H)$^+$: 303. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{24}FN_2O_4$ 303.1720; found 303.1727.

*4a-(Trifluoromethyl)octahydrothiopyrano[2,3-c]pyrrole 1,1-Dioxide (**38c**).* General procedure F. The final product was crystallized from benzene. Yield: 21.14 g, 0.087 mol, 87%, white solid, mp = 133−134 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 3.71 (dd, J = 13.0, 3.4 Hz, 1H), 3.47 (dd, J = 7.6, 3.6 Hz, 1H), 3.36 (dd, J = 13.1, 7.7 Hz, 1H), 3.27 (d, J = 12.4 Hz, 1H), 3.18−3.08 (m, 1H), 3.05−2.95 (m, 2H), 2.39−2.07 (m, 4H), 2.04−1.86 (m, 1H) ppm. $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 127.8 (q, J = 282.6 Hz), 61.9, 55.8, 55.0 (q, J = 24.2 Hz), 48.6, 46.4, 23.4, 18.6 ppm. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$): δ −74.1 (s) ppm. LCMS (M + H)$^+$: 244. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_8H_{13}F_3NO_2S$ 244.0619; found 244.0605.

*7a-(Trifluoromethyl)octahydrothiopyrano[2,3-c]pyrrole 1,1-dioxide Hydrochloride (**40c**).* General procedure F. The final product was crystallized from *i*-PrOH. Yield: 23.48 g, 0.084 mol, 84%, white solid, mp = 160−162 °C. ^1H NMR (400 MHz, DMSO-d_6): δ 10.41 (br s, 2H), 3.95 (d, J = 14.3 Hz, 1H), 3.71 (br s, 1H), 3.65 (d, J = 14.4 Hz, 1H), 3.55−3.30 (m, 4H), 3.30−3.19 (m, 1H), 2.20−1.99 (m, 2H), 1.97−1.84 (m, 1H), 1.86−1.70 (m, 1H) ppm. $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6): δ 123.4 (q, J = 282.6 Hz), 70.0 (q, J = 26.2 Hz), 50.5, 46.7, 44.2, 40.7, 19.0 ppm. $^{19}F\{^1H\}$ NMR (376 MHz, DMSO-d_6): δ −65.9 (s) ppm. LCMS (M + H)$^+$: 244. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_8H_{13}F_3NO_2S$ 244.0619; found 244.0610.

General procedure G for synthesis of 2d, 6d, 7d, 23d−25d, 28d, and 29d. See **2d** as an example. Scale: 0.05 mol.

*tert-Butyl (3-Azabicyclo[3.2.0]heptan-1-yl)carbamate (**2d**).* To a solution of **2a** (12.25 g, 0.05 mol, 1.0 equiv) in MeOH (100 mL) was added NaOH (4.00 g, 0.1 mol, 2.0 equiv). The solution was stirred at rt overnight. The solution was concentrated under reduced pressure. The residue was washed with methyl *tert*-butyl ether (2 × 50 mL) and then acidified with 1 M HCl to pH ∼ 4. The solution was extracted with EtOAc (3 × 100 mL). The combined fractions were washed with brine (1 × 100 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure.The crude product was dissolved in *t*-BuOH (150 mL), and Et_3N (7.6 mL, 0.055 mol, 1.1 equiv) was added. The solution was heated to boiling, and $(PhO)_2PON_3$ (13.80 g, 0.05 mol, 1.0 equiv) was added dropwise. The solution was heated at reflux in an oil bath with a thermocouple for 5 h. After heating was stopped, the mixture was concentrated under reduced pressure, and the residue was dissolved in methyl *tert*-butyl ether (200 mL). The solution was washed with saturated solution of $NaHCO_3$ (1 × 100 mL). The aqueous layer was additionally extracted with methyl *tert*-butyl ether (1 × 100 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was dissolved in MeOH (100 mL) and Pd/C (10%), (1.00 g) was added to the solution. The mixture was hydrogenated under a rubber ball filled with H_2 at rt for 1 d. Pd/C was filtered, and the reaction mixture was concentrated under reduced pressure to give the desired product as a white solid, mp = 112−113 °C. Yield: 4.3 g, 0.02 mol, 41%. ^1H NMR (400 MHz, $CDCl_3$): δ 4.94 (br s, 1H), 3.06 (d, J = 11.2 Hz, 1H), 2.99 (dd, J = 11.1, 5.5 Hz, 1H), 2.80−2.72 (m, 2H), 2.37 (br s, 1H), 2.25−2.08 (m, 2H), 2.05−1.91 (m, 1H), 1.42 (s, 9H), 1.36−1.26 (m, 1H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 154.8, 79.4, 62.6, 59.6, 53.8, 43.8, 30.6, 28.5, 19.4 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{11}H_{21}N_2O_2$ 213.1603; found 213.1579.

*tert-Butyl (Hexahydrocyclopenta[c]pyrrol-3a(1H)-yl)carbamate (**6d**).* General procedure G. Yield: 4.97 g, 0.022 mol, 44%, white oil. ^1H NMR (400 MHz, $CDCl_3$): δ 4.87 (br s, 1H), 3.36−3.10 (m, 2H), 2.76 (d, J = 11.8 Hz, 1H), 2.52−2.39 (m, 1H), 2.35 (br s, 1H), 2.20 (br s, 1H), 1.97−1.74 (m, 3H), 1.72−1.51 (m, 2H), 1.41 (s, 9H), 1.36−1.28 (m, 1H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 155.2, 79.2, 72.3, 69.4, 60.6, 54.8, 52.4, 39.4, 31.8, 28.6, 25.8 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{12}H_{23}N_2O_2$ 227.1760; found 227.1751.

*tert-Butyl (6a-Fluorohexahydrocyclopenta[c]pyrrol-3a(1H)-yl)-carbamate Hydrochloride (**7d**).* General procedure G. The residue was dissolved in EtOAc (50 mL), and 1 M HCl in EtOAc (50 mL) was added dropwise. The mixture was stirred for 0.5 h and filtered. Yield: 4.49 g, 0.016 mol, 32%, white solid, mp = 60−62 °C. ^1H NMR (400 MHz, DMSO-d_6): δ 9.75 (br s, 2H), 7.15 (br s, 1H), 3.76−3.57 (m, 2H), 3.38 (d, J = 13.4 Hz, 1H), 3.32 (d, J = 13.3 Hz, 1H), 3.16 (d, J = 12.6 Hz, 1H), 2.23−2.08 (m, 1H), 2.05−1.82 (m, 3H), 1.80−1.65 (m, 1H), 1.62−1.48 (m, 1H), 1.40 (s, 9H) ppm. $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6): δ 155.6, 106.2 (d, J = 203.9 Hz), 78.9, 67.5 (d, J = 15.7 Hz), 53.6, 53.3, 35.8, 34.9 (d, J = 23.6 Hz), 28.1, 20.3 (d, J = 6.3 Hz) ppm. $^{19}F\{^1H\}$ NMR (376 MHz, DMSO-d_6): δ −151.8 (s) ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{12}H_{22}FN_2O_2$ 245.1665; found 245.1649.

*tert-Butyl (2,2-Dioxidotetrahydro-1H-thieno[3,4-c]pyrrol-3a(3H)-yl)carbamate (**23d**).* General procedure G. Yield: 6.76 g, 0.0245 mol, 49%, white solid, mp = 195−196 °C. ^1H NMR (400 MHz, DMSO-d_6): δ 7.46 (s, 1H), 3.46−3.36 (m, 2H), 3.22 (d, J = 14.2 Hz, 1H), 3.10 (dd, J = 11.2, 8.0 Hz, 1H), 3.01−2.90 (m, 3H), 2.82−2.73 (m, 1H), 2.72 (br s, 1H), 2.58 (dd, J = 11.5, 5.0 Hz, 1H), 1.39 (s, 9H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6): δ 155.0, 78.4, 65.2, 60.3, 57.1, 53.6, 52.4, 46.0, 28.2 ppm. LCMS (M + H)$^+$: 277. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{11}H_{21}N_2O_4S$ 277.1222; found 277.1241.

*tert-Butyl (Octahydro-3aH-isoindol-3a-yl)carbamate (**24d**).* General procedure G. Yield: 6.36 g, 0.0265 mol, 53%, white solid, mp = 91−92 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 4.70 (s, 1H), 3.15 (d, J = 11.4 Hz, 1H), 3.09 (dd, J = 10.6, 7.6 Hz, 1H), 2.99 (d, J = 11.3 Hz, 1H), 2.78 (dd, J = 10.6, 6.6 Hz, 1H), 2.42 (br s, 1H), 2.14 (br s, 1H), 1.98 (br s, 1H), 1.78−1.41 (m, 7H), 1.40 (s, 9H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 154.8, 79.1, 60.5, 55.8, 49.7, 43.1, 29.6, 28.5, 25.7, 22.2, 22.1 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{13}H_{25}N_2O_2$ 241.1916; found 241.1902.

*tert-Butyl (6,6-Difluorooctahydro-3aH-isoindol-3a-yl)carbamate (**25d**).* General procedure G. Yield: 7.31 g, 0.0265 mol, 53%, yellow oil. ^1H NMR (400 MHz, DMSO-d_6): δ 6.92 (s, 1H), 3.31 (br s, 1H), 3.02 (d, J = 11.3 Hz, 1H), 2.96−2.86 (m, 1H), 2.80 (d, J = 11.3 Hz, 1H), 2.65−2.56 (m, 1H), 2.41−2.29 (m, 1H), 2.19−2.05 (m, 2H), 1.90−1.70 (m, 4H), 1.38 (s, 9H) ppm. $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6): δ 154.6, 124.2 (t, J = 240.2 Hz), 77.6, 58.8, 55.2, 49.1, 41.1, 31.9 (t, J = 22.7 Hz), 29.5 (t, J = 23.9 Hz), 28.2, 25.6 ppm. $^{19}F\{^1H\}$ NMR (376 MHz, DMSO-d_6): δ −89.60 − −92.26 (m, 2F) ppm. LCMS (M + H)$^+$: 277. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{13}H_{23}F_2N_2O_2$ 277.1728; found 277.1720.

*tert-Butyl (Hexahydropyrano[3,4-c]pyrrol-7a(1H)-yl)carbamate (**28d**).* General procedure G. Yield: 6.41 g, 0.0265 mol, 53%, white solid, mp = 100−101 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 4.77 (br s, 1H), 3.70−3.51 (m, 4H), 3.24−3.05 (m, 3H), 2.93 (dd, J = 10.8, 7.6 Hz, 1H), 2.19 (br s, 1H), 2.13−1.99 (m, 2H), 1.98−1.83 (m, 1H), 1.41 (s, 9H) ppm. $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 154.8, 79.7, 65.3, 64.4, 57.7, 56.3, 47.1, 43.6, 30.2, 28.5 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{12}H_{23}N_2O_3$ 243.1709; found 243.1726.

*tert-Butyl (Hexahydropyrano[3,4-c]pyrrol-3a(4H)-yl)carbamate (**29d**).* General procedure G. Yield: 4.48 g, 0.0185 mol, 37%, white solid, mp = 133−134 °C. ^1H NMR (400 MHz, DMSO-d_6): δ 6.82 (s, 1H), 3.70 (d, J = 11.6 Hz, 1H), 3.61−3.48 (m, 2H), 3.47−3.32 (m, 1H), 3.23 (br s, 1H), 3.03−2.94 (m, 2H), 2.85 (d, J = 11.4 Hz, 1H), 2.65 (dd, J = 10.3, 5.3 Hz, 1H), 2.24 (br s, 1H), 1.81−1.69 (m, 1H), 1.37 (s, 9H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6): δ 154.7, 77.6, 67.4, 64.3, 58.4, 52.7, 49.1, 28.2, 25.1 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{12}H_{23}N_2O_3$ 243.1709; found 243.1702.

General Procedure H for Synthesis of 2e, 6e, 7e, 9e, 10e, 12e, 14e, 24e, 26e, 31e, and 32e. See **2e** as an example. Scale: 0.05 mol. Note: Amines **7e**, **12e**, **26e**, and **32e** were treated with 1 M HCl in dioxane, and the precipitate was filtered off to obtain amines hydrochlorides.

*3-Azabicyclo[3.2.0]heptan-1-yl)methanol (**2e**).* A solution of **2a** (12.25 g, 0.05 mol, 1.0 equiv) in Et_2O (50 mL) was added dropwise to a suspension of $LiAlH_4$ (1.20 g, 0.03 mol, 0.6 equiv) in (100 mL) at 0−10 °C. Then the reaction mixture was warmed to rt and allowed to

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stir overnight. The mixture was quenched with water (1.1 mL, 0.06 mol, 1.2 equiv) and an aq solution of NaOH (4.80 g, 0.12 mol, 2.4 equiv). The mixture was filtered through a thick pad of Na_2SO_4. The solid residue was washed with hot THF (100 mL). The filtrated was concentrated. The crude product was dissolved in MeOH (100 mL), and Pd/C (10%), (1.00 g) was added to the solution. The mixture was hydrogenated under a rubber ball filled with H_2 overnight at rt. Pd/C was filtered, and the reaction mixture was concentrated under reduced pressure to give the desired product as a white gum. Yield: 4.51 g, 0.036 mol, 71%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.66 (d, J = 10.9 Hz, 1H), 3.58 (d, J = 10.8 Hz, 1H), 3.16 (br s, 2H), 2.89−2.71 (m, 3H), 2.60 (d, J = 11.3 Hz, 1H), 2.52−2.42 (m, 1H), 2.18−1.88 (m, 2H), 1.73−1.54 (m, 1H), 1.48−1.33 (m, 1H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 66.8, 56.8, 54.5, 51.4, 40.2, 25.9, 20.8 ppm. LCMS (M + H)$^+$: 128. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_7H_{14}NO$ 128.1075; found 128.1061.

*Hexahydrocyclopenta[c]pyrrol-3a(1H)-yl)methanol (**6e**).* General procedure H. Yield: 5.36 g, 0.038 mol, 76%, yellow gum. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.27 (d, J = 10.3 Hz, 1H), 3.23 (d, J = 10.3 Hz, 1H), 2.88 (dd, J = 10.7, 7.9 Hz, 1H), 2.73 (d, J = 10.9 Hz, 1H), 2.32 (d, J = 11.2 Hz, 1H), 2.30−2.24 (m, 1H), 2.02−1.91 (m, 1H), 1.67−1.38 (m, 4H), 1.35−1.19 (m, 2H) ppm. ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6): δ 67.3, 57.4, 57.3, 54.5, 35.2, 32.1, 25.5 ppm. GCMS (M): 141. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_8H_{16}NO$ 142.1232; found 142.1238.

*6a-Fluorohexahydrocyclopenta[c]pyrrol-3a(1H)-yl)methanol Hydrochloride (**7e**).* General procedure H. Yield: 7.13 g, 0.037 mol, 73%, white solid, mp = 105−106 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.96 (br s, 1H), 9.65 (br s, 1H), 4.56 (br s, 1H), 3.57−3.26 (m, 5H), 3.02−2.87 (m, 1H), 2.22−2.05 (m, 1H), 1.99−1.83 (m, 1H), 1.80−1.66 (m, 2H), 1.66−1.58 (m, 2H) ppm. ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 109.6 (d, J = 196.4 Hz), 61.9 (d, J = 14.3 Hz), 55.8 (d, J = 17.3 Hz), 53.8 (d, J = 32.5 Hz), 52.5, 35.7 (d, J = 24.3 Hz), 33.0, 21.6 (d, J = 5.7 Hz) ppm. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6): δ −159.8 (s) ppm. LCMS (M + H)$^+$: 160. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_8H_{15}FNO$ 160.1138; found 160.1145.

*(Tetrahydro-1H-furo[3,4-c]pyrrol-3a(3H)-yl)methanol (**10e**).* General procedure H. Yield: 4.58 g, 0.032 mol, 64%, white solid, mp = 89−90 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.87 (dd, J = 8.8, 7.5 Hz, 1H), 3.67 (t, J = 8.8 Hz, 1H), 3.64−3.51 (m, 4H), 3.11 (dd, J = 11.0, 7.5 Hz, 1H), 2.98 (d, J = 11.1 Hz, 1H), 2.90 (br s, 2H), 2.80 (d, J = 11.1 Hz, 1H), 2.70 (dd, J = 11.1, 4.5 Hz, 1H), 2.46−2.36 (m, 1H) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 76.2, 74.3, 66.6, 59.4, 56.2, 53.6, 48.8 ppm. LCMS (M + H)$^+$: 144. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_7H_{14}NO_2$ 144.1025; found 144.1031.

*Hexahydro-6aH-furo[2,3-c]pyrrol-6a-yl)methanol Hydrochloride (**12e**).* General procedure H. Yield: 5.96 g, 0.031 mol, 61%, orange gum. ^{1}H NMR (400 MHz, D_2O): δ 4.05 (dd, J = 14.9, 7.6 Hz, 1H), 3.93 (dd, J = 15.5, 7.2 Hz, 1H), 3.72 (d, J = 12.1 Hz, 1H), 3.67 (d, J = 12.1 Hz, 1H), 3.61−3.49 (m, 1H), 3.45 (d, J = 12.8 Hz, 1H), 3.37 (d, J = 12.8 Hz, 1H), 3.31 (dd, J = 12.3, 4.3 Hz, 1H), 3.05−2.87 (m, 1H), 2.41−2.22 (m, 1H), 1.96−1.82 (m, 1H) ppm. ^{13}C{^{1}H} NMR (151 MHz, D_2O): δ 92.5, 68.1, 62.6 52.6, 51.0, 43.0, 31.5 ppm. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_7H_{14}NO_2$ 144.1025; found 144.1016.

*Hexahydropyrrolo[3,4-c]pyrrol-3a(1H)-yl)methanol (**14e**).* General procedure H. Yield: 5.75 g, 0.041 mol, 81%, white solid, mp = 63−64 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.57−3.42 (m, 2H), 3.09−3.02 (m, 2H), 2.98 (br s, 2H), 2.89−2.85 (m, 2H), 2.72−2.63 (m, 2H), 2.64−2.52 (m, 2H), 2.36−2.21 (m, 1H) ppm. ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 67.7, 67.6, 58.8, 58.7, 56.4, 56.4, 53.7, 48.7, 48.6 ppm. LCMS (M + H)$^+$: 143. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_7H_{15}N_2O$ 143.1184; found 143.1169.

*Octahydro-3aH-isoindol-3a-yl)methanol (**24e**).* General procedure H. Yield: 6.43 g, 0.042 mol, 83%, white gum. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.36 (d, J = 10.6 Hz, 1H), 3.13 (d, J = 10.6 Hz, 1H), 2.86 (dd, J = 10.1, 7.6 Hz, 1H), 2.63 (dd, J = 10.1, 6.6 Hz, 1H), 2.54 (br s, 2H), 1.76−1.69 (m, 1H), 1.54−1.17 (m, 9H) ppm. ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 65.7, 54.5, 50.2, 45.2, 38.8, 27.2, 25.3, 22.2, 21.5 ppm. LCMS (M + H)$^+$: 156. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_9H_{18}NO$ 156.1388; found 156.1380.

*Hexahydropyrano[2,3-c]pyrrol-4a(2H)-yl)methanol Hydrochloride (**26e**).* To a mixture of **26a** (5.22 g, 19.0 mmol) in THF (100 mL) and ethanol (25 mL) was added $NaBH_4$ (2.17 g, 57.4 mmol, 3 equiv) followed by addition of LiCl (2.43 g, 58.6 mmol, 3 equiv) at 0 °C. The mixture was stirred at room temperature for 12 h and quenched with saturated aq NH_4Cl (50 mL), and the pH value of the reaction mixture was adjusted to 9 by adding 1 M aq NaOH. The reaction mixture was extracted with CH_2Cl_2 (3 × 150 mL). The combined organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was dissolved in MeOH (50 mL) and 10% Pd/C (500 mg) was added to the solution. The mixture was hydrogenated in an autoclave at 10 atm (H_2), 50 °C during 15 h. The catalyst was filtered off, and the reaction mixture was concentrated under reduced pressure. The residue was dissolved in dioxane (50 mL), and an excess of 1 M HCl in dioxane was added. The reaction mixture was evaporated under vacuum to provide product **26e** as a yellow gum. Yield: 2.61 g, 13.5 mmol, 71%. ^{1}H NMR (400 MHz, D_2O): δ 4.04 (d, J = 3.5 Hz, 1H), 3.95−3.87 (m, 1H), 3.61 (dd, J = 13.0, 3.3 Hz, 1H), 3.44 (s, 2H), 3.44−3.18 (m, 4H), 1.87−1.38 (m, 4H) ppm. ^{13}C{^{1}H} NMR (126 MHz, D_2O): δ 78.2, 65.9, 65.7, 51.3, 46.9, 45.5, 23.0, 19.7 ppm. LCMS (M + H)$^+$: 158. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_8H_{16}NO_2$ 158.1181; found 158.1177.

*5-Methyloctahydro-7aH-pyrrolo[3,4-c]pyridin-7a-yl)methanol Dihydrochloride (**32e**).* General procedure H. Yield: 5.26 g, 0.026 mol, 51%, white solid, mp = 192−193 °C. ^{1}H NMR (400 MHz, D_2O): δ 3.83−3.11 (m, 10H), 2.94, 2.92 (2 × s, 3H), 2.89−2.71 (m, 2H), 2.16−1.85 (m, 2H) ppm. ^{13}C{^{1}H} NMR (151 MHz, D_2O): δ 66.0, 61.4, 52.9, 52.5, 49.8, 49.0, 48.0, 46.9, 45.8, 43.3, 43.1, 43.0, 41.5, 36.8, 35.7, 24.1, 23.7 ppm. LCMS (M + H)$^+$: 171. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_9H_{19}N_2O$ 171.1497; found 171.1476.

*tert-Butyl (Hexahydro-6aH-furo[2,3-c]pyrrol-6a-yl)methyl)-carbamate Hydrochloride (**15f**).* A solution **15a** (11.40 g, 0.05 mol, 1.0 equiv) in 200 mL of MeOH−NH_3 (17%) was reduced in autoclave with Raney nickel at 50 atm, 8 h. The mixture was filtered and concentrated under reduced pressure. The resulting amine was dissolved in EtOAc (150 mL) and triturated with 5 M HCl in dioxane. The solid residue was dissolved in CH_2Cl_2 (200 mL), and Et_3N (10.10 g, 0.1 mol, 2.0 equiv) was added to the mixture. Then Boc_2O (10.90 g, 0.05 mol, 1.0 equiv) in CH_2Cl_2 (20 mL) was added dropwise at rt (the mixture can be cooled in a water bath). The solution was stirred overnight at rt. The mixture was washed with 0.5 M HCl (1 time), water (1 time), and brine and dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The oily product was dissolved in MeOH (100 mL), and Pd/C (10%), (1.00 g) was added to the solution. The mixture was hydrogenated under a rubber ball filled with H_2 overnight at rt. Pd/C was filtered, and the reaction mixture was concentrated under reduced pressure. The residue was dissolved in EtOAc (100 mL), and 1 M HCl in EtOAc (100 mL) was added dropwise. The mixture was stirred for 0.5 h and filtered. Yield: 8.91 g, 0.032 mol, 64%, white solid, mp = 182−183 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.81 (br s, 1H), 9.46 (br s, 1H), 3.98−3.88 (m, 1H), 3.80−3.70 (m, 1H), 3.35 (s, 1H), 3.32−3.24 (m, 1H), 3.20−3.08 (m, 4H), 3.03 (dd, J = 12.0, 4.4 Hz, 1H), 2.83−2.71 (m, 1H), 2.14−2.01 (m, 1H), 1.91−1.80 (m, 1H), 1.38 (s, 9H) ppm. ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 156.1, 92.1, 78.0, 67.3, 52.1, 49.9, 43.3, 43.0, 31.3, 28.2 ppm. LCMS (M + H)$^+$: 243. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{12}H_{23}N_2O_3$ 243.1709; found 243.1718.

*tert-Butyl (Hexahydropyrano[3,4-c]pyrrol-7a(1H)-yl)methyl)-carbamate (**27f**).* The same procedure as for **15f** was applied. The product was obtained as a free base. HCl in EtOAc was not added at the end. Yield: 8.70 g, 0.034 mol, 68%, white solid, mp = 82−83 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.60−3.41 (m, 4H), 3.28−3.13 (m, 2H), 3.01 (dd, J = 13.8, 6.0 Hz, 2H), 2.85 (br s, 2H), 1.86 (br s, 1H), 1.77 (br s, 2H), 1.61−1.49 (m, 1H), 1.37 (s, 9H) ppm. ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 156.5, 78.1, 63.3, 52.8, 45.3, 42.9,

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28.3, 27.1 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{13}H_{25}N_2O_3$ 257.1865; found 257.1860.

*3a-(Methoxymethyl)hexahydro-2H-furo[2,3-c]pyrrole Hydrochloride (**9g**).* Compound **9e** (2.20 g, 0.014 mol, 1.0 equiv; **9e** was obtained from **9a** following the same protocol that was used in the transformation **26a** → **26e**) was dissolved in CH_2Cl_2 (50 mL) and Et_3N (1.56 g, 0.015 mol, 1.1 equiv) was added to the mixture. Then Boc_2O (3.36 g, 0.15 mol, 1.1 equiv) in CH_2Cl_2 (10 mL) was added dropwise at rt. The solution was stirred overnight at rt. The mixture was washed with 0.5 M HCl (1 × 10 mL), water (1 × 10 mL), brine (1 × 20 mL) and dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was dissolved in THF (100 mL) and NaH (60% in oil, 1.12 g, 0.028 mol, 2 equiv) was added. Then MeI (5.96 g, 0.42 mol, 3.0 equiv) was added dropwise at 0 °C. The mixture was stirred overnight and quenched with water (10 mL), diluted with EtOAc and water. The organic layer was separated and the aqueous was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with brine (2 × 50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was dissolved in EtOAc (50 mL), and 1 M HCl in EtOAc (20 mL) was added dropwise. The mixture was stirred for 0.5 h and filtered. Yield: 1.92 g, 0.01 mol, 71%, yellow solid, mp = 72−73 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.80 (br s, 1H), 9.43 (br s, 1H), 4.21 (d, J = 4.4 Hz, 1H), 3.94 (dd, J = 14.8, 6.3 Hz, 1H), 3.66 (dd, J = 15.8, 7.2 Hz, 1H), 3.43 (s, 2H), 3.34 (s, 1H), 3.30 (s, 3H), 3.29−3.23 (m, 1H), 3.16−3.10 (m, 2H), 1.97−1.88 (m, 2H) ppm. ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 83.9, 74.4, 67.5, 58.7, 54.6, 51.9, 50.5, 35.5 ppm. LCMS $(M + H)^+$: 158. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_8H_{16}NO_2$ 158.1181; found 158.1175.

*6a-(Methoxymethyl)hexahydro-2H-furo[2,3-c]pyrrole Hydrochloride (**12g**).* The same procedure as for **9g** was used. Yield: 1.20 g, 0.006 mol, 44%, yellow solid, mp = 139−140 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.77 (br s, 1H), 9.42 (br s, 1H), 3.92 (dd, J = 13.7, 6.8 Hz, 1H), 3.75 (dd, J = 13.5, 6.7 Hz, 1H), 3.42 (s, 2H), 3.34 (s, 1H), 3.30 (s, 3H), 3.15 (s, 2H), 3.11−3.02 (m, 1H), 2.81−2.68 (m, 1H), 2.15−2.00 (m, 1H), 1.87−1.77 (m, 1H) ppm. ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 91.3, 73.5, 67.6, 58.9, 51.8, 49.8, 43.5, 31.4 ppm. LCMS $(M + H)^+$: 158. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_8H_{16}NO_2$ 158.1181; found 158.1175.

*5-(Tetrahydro-1H-furo[3,4-c]pyrrol-3a(3H)-yl)-1,3,4-oxadiazol-2-amine Hydrochloride (**10h**).* Semicarbazide hydrochloride (4.46 g, 0.04 mol, 2.0 equiv) was slowly added to a solution of **10b** (5.14 g, 0.02 mol, 1.0 equiv) in phosphorus oxychloride (30 mL). The mixture was stirred at room temperature overnight and then poured into crushed ice (100 g). A viscous solid was decanted from the aqueous layer, and then the aqueous layer was adjusted to pH 4 to 5 with sodium hydroxide (50% aqueous solution). The resulting precipitate was filtered. The residue was dissolved in 5 M HCl in dioxane, and the precipitate was filtered and dried. Yield: 4.10 g, 0.0176 mol, 88%, white solid, mp = 219−221 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.17 (br s, 1H), 8.55 (br s, 1H), 6.73 (br s, 2H), 4.06 (d, J = 9.5 Hz, 1H), 3.99 (d, J = 9.5 Hz, 1H), 3.93 (dd, J = 9.1, 7.2 Hz, 1H), 3.84 (dd, J = 9.3, 4.4 Hz, 1H), 3.69 (dd, J = 12.0, 6.0 Hz, 1H), 3.53−3.45 (m, 1H), 3.45−3.33 (m, 2H), 3.19 (dd, J = 10.1, 3.9 Hz, 1H) ppm. ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 161.9, 158.9, 75.1, 72.5, 53.1, 51.2, 49.1, 48.5 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_8H_{13}N_4O_2$ 197.1039; found 197.1016.

*tert-Butyl 3-benzyl-3,6-diazabicyclo[3.2.0]heptane-6-carboxylate (**42a**).* Protocol C was applied. Scale: 0.01 mol. Yield: 350 mg, 1.2 mmol, 12%, pale yellow oil. Purified by column chromatography twice (hexane/ methyl *tert*-butyl ether = 7:3), $CHCl_3$:CH_3CN (85:15). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.54−6.97 (m, 5H), 4.53 (m, 1H), 3.91 (m, 1H), 3.56 (m, 3H), 3.19 (m, 1H), 2.87 (m, 2H), 2.07 (m, 1H), 1.96 (m, 1H), 1.33 (2 × s, 9H). ^{13}C{^{1}H} NMR of both Boc-rotamers (126 MHz, $CDCl_3$): δ 155.2, 139.1, 128.7, 128.3, 127.0, 79.2, 65.9, 65.0, 59.0, 57.9, 57.5, 57.3, 57.0, 54.0, 52.6, 33.18, 33.1, 28.6 ppm LCMS $(M + H)^+$: 289. Anal. Calcd for $C_{17}H_{24}N_2O_2$: C, 70.80; H, 8.39; N, 9.71. Found: C, 71.13; H, 8.66; N, 9.44.

*3-Benzyl-6-thia-3-azabicyclo[3.2.0]heptane 6,6-Dioxide (**45a**).* Protocol A was used. The residue was purified by column chromatography (hexane/EtOAc/Et_3N = 1:1:0.2). Yield: 19.90 g, 0.084 mol, 84%, white solid. mp = 76−77 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.43−7.29 (m, 4H), 7.25 (t, J = 6.8 Hz, 1H), 4.65 (t, J = 6.9 Hz, 1H), 4.31−4.19 (m, 1H), 3.87 (dd, J = 13.4, 5.8 Hz, 1H), 3.76 (d, J = 13.7 Hz, 1H), 3.65 (d, J = 13.7 Hz, 1H), 3.36−3.32 (m, 1H), 3.04−2.94 (m, 1H), 2.89 (d, J = 9.3 Hz, 1H), 2.36−2.21 (m, 2H) ppm. ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6): δ 138.4, 128.2, 128.1, 126.9, 80.5, 70.2, 57.4, 57.2, 53.3, 24.2 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{12}H_{16}NO_2S$ 238.0902; found 238.0928.

*5-Benzylhexahydro-2H-thieno[2,3-c]pyrrole 1,1-Dioxide (**46a**).* Modified protocol C was used, 70 °C, 3 days. The residue was purified by column chromatography (hexane/EtOAc/Et_3N = 1:1:0.2). Yield: 18.07 g, 0.072 mol, 72%, yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42−7.24 (m, 5H), 3.71 (d, J = 13.1 Hz, 1H), 3.57−3.44 (m, 2H), 3.34 (t, J = 7.7 Hz, 1H), 3.22−3.08 (m, 2H), 3.08−2.97 (m, 1H), 2.71 (d, J = 9.1 Hz, 1H), 2.57−2.45 (m, 2H), 2.41−2.27 (m, 1H), 2.07−1.93 (m, 1H) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 138.2, 128.5, 128.5, 127.3, 61.6, 60.9, 59.0, 56.0, 50.0, 39.5, 27.4 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{13}H_{18}NO_2S$ 252.1058; found 252.1065.

*6-Benzyloctahydrothiopyrano[2,3-c]pyrrole 1,1-Dioxide (**47a**).* Modified protocol C was used. The mixture was heated at 70 °C for 48 h. Ca. 50% conversion was observed according to ^{1}H NMR. An additional portion of **1** (35.55 g, 0.15 mol, 1.5 equiv) was added. The mixture was heated for 48 h. The residue was purified by column chromatography (hexane/EtOAc/Et_3N = 1:1:0.2). Yield: 18.55 g, 0.07 mol, 70%, yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36−7.25 (m, 5H), 3.75 (d, J = 2.2 Hz, 2H), 3.59−3.47 (m, 1H), 3.23 (dd, J = 11.2, 6.6 Hz, 1H), 3.15−2.99 (m, 2H), 2.99−2.89 (m, 1H), 2.84−2.68 (m, 3H), 2.22−2.00 (m, 2H), 1.89−1.71 (m, 2H) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 138.8, 128.7, 128.5, 127.3, 61.7, 59.9, 58.2, 51.3, 48.9, 39.7, 24.9, 21.7 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{20}NO_2S$ 266.1215; found 266.1202.

*6-Thia-3-azabicyclo[3.2.0]heptane 6,6-Dioxide (**45c**).* General procedure F. Yield: 14.06 g, 0.095 mol, 95%, white solid. mp = 85−86 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.61 (t, J = 7.4 Hz, 1H), 4.27−4.15 (m, 1H), 3.80 (dd, J = 13.6, 6.0 Hz, 1H), 3.42 (d, J = 13.1 Hz, 1H), 3.00−2.92 (m, 2H), 2.79 (dd, J = 13.1, 7.2 Hz, 2H), 2.61 (dd, J = 11.4, 5.3 Hz, 1H) ppm. ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 82.4, 68.7, 52.1, 48.5, 26.0 ppm. LCMS $(M + H)^+$: 148. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_5H_{10}NO_2S$ 148.0432; found 148.0426.

*Hexahydro-2H-thieno[2,3-c]pyrrole 1,1-Dioxide Hydrochloride (**46c**).* General procedure F. 1 M HCl in dioxane (50 mL) was added to the product, and the formed hydrochloride was filtered off. Yield: 17.78 g, 0.09 mol, 90%, white solid, mp = 226−227 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.88 (s, 2H), 3.84−3.74 (m, 1H), 3.65−3.48 (m, 2H), 3.43−3.29 (m, 3H), 3.28−3.18 (m, 1H), 3.11 (q, J = 9.2 Hz, 1H), 2.29−2.13 (m, 1H), 2.03−1.89 (m, 1H) ppm. ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 60.1, 49.4, 49.1, 44.9, 40.2, 23.4 ppm. LCMS $(M + H)^+$: 162. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_6H_{12}NO_2S$ 162.0589; found 162.0572.

*Octahydrothiopyrano[2,3-c]pyrrole 1,1-Dioxide Hydrochloride (**47c**).* General procedure F. 1 M HCl in dioxane (50 mL) was added to the product, and the formed hydrochloride was filtered off. Yield: 19.46 g, 0.092 mol, 92%, white solid, mp = 228−229 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.87 (br s, 2H), 3.99−3.85 (m, 1H), 3.61 (dd, J = 13.0, 5.2 Hz, 1H), 3.50 (dd, J = 12.9, 8.0 Hz, 1H), 3.29−3.11 (m, 4H), 2.86−2.74 (m, 1H), 2.09−1.85 (m, 2H), 1.85−1.60 (m, 2H) ppm. ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 59.6, 48.5, 47.2, 42.0, 39.0, 21.4, 20.5 ppm. LCMS $(M + H)^+$: 176. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd $C_7H_{14}NO_2S$ 176.0745; found 176.0732.

*tert-Butyl 3,6-Diazabicyclo[3.2.0]heptane-6-carboxylate Hydrochloride (**50**).* Compound **42a** (200 mg, 1 mmol) was dissolved in MeOH (50 mL), and Pd/C (10%) (10 mg) was added to the solution. The mixture was hydrogenated under a rubber ball filled with H_2 overnight at rt. Pd/C was filtered, and the reaction mixture was concentrated under reduced pressure. The residue was dissolved in EtOAc (1 mL), 1 M HCl EtOAc (1 mL) was added dropwise, and

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the precipitate was filtered and dried. Yield: 222 mg, 0.95 mmol, 95%, white solid, mp = 158−160 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.74 (br s, 2H), 4.98−4.52 (m, 1H), 3.98−3.76 (m, 1H), 3.61 (m, 1H), 3.49−3.25 (m, 2H), 3.25−2.76 (m, 3H), 1.32 (s, 9H) ppm. ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 154.9, 154.4, 79.5, 65.2, 64.3, 52.8, 51.5, 49.7, 49.4, 49.1, 32.9, 28.6 ppm. LCMS (M-Cl)$^-$: 199. Anal. Calcd for $C_{10}H_{19}ClN_2O_2$: C, 51.17; H, 8.16; N, 11.93. Found: C, 50.86; H, 8.41; N, 11.64.

*tert-Butyl (3aS,7aS)-2-Benzyl-7a-(dimethylphosphoryl)-octahydro-5H-pyrrolo[3,4-c]pyridine-5-carboxylate (**53a**).*[31] Protocol D was used. Yield: 314 mg, 0.8 mmol, 80%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34−7.19 (m, 5H), 3.87−3.39 (m, 5H), 3.18 (dd, J = 21.6, 14.0 Hz, 1H), 3.02−2.76 (m, 2H), 2.70−2.52 (m, 1H), 2.43−2.13 (m, 3H), 1.65 (d, J = 14.5 Hz, 1H), 1.54−1.35 (m, 15H) ppm. ^{13}C{^{1}H} NMR both Boc-rotamers (151 MHz, $CDCl_3$): δ 156.0, 155.7, 138.8, 138.7, 128.6, 128.50, 128.47, 127.3, 79.8, 79.7, 59.8, 58.2, 58.2, 57.8, 57.5, 41.3, 40.8, 39.6, 38.9, 38.8, 38.4, 38.3, 38.2, 38.1, 28.6, 28.6, 24.2, 24.0, 12.5 (m) ppm. ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 52.6, 52.5 ppm. LCMS (M + H)$^+$: 393. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd $C_{21}H_{34}N_2O_3P$ 393.2307; found 393.2301.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c01327.

Copies of NMR spectra, pK_a determination, and X-ray crystallographic data (PDF)

Accession Codes

CCDC 2077600−2077602 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

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