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# Synthesis of 6-azaspiro[4.3]alkanes: innovative scaffolds for drug discovery

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**Abstract:** Novel scaffolds for drug discovery -6-azaspiro[4.3]alkanes - have been synthesized in two steps from four-membered ketones: cyclobutanone, thienone, N-Bocazetidinone, *etc.* The key transformation was the reaction between electron-deficient exocyclic alkenes with *in situ* generated *N*-benzyl azomethine ylide. with improved physico-chemical characteristics.<sup>6</sup> Since then, spirocyclic compounds have been playing an important role in medicinal chemistry (Figure 1).<sup>7-9</sup> In this work, therefore, we have developed a synthetic approach towards a new generation of spirocycles - 6-azaspiro[4.3]alkanes (Figure 1).

### Introduction

Trends in drug discovery have been changing rapidly. During the past decade, terms "*Scaffold hopping*,"<sup>1</sup> "*Escape the Flatland*"<sup>2</sup> and "*Conformational restriction*"<sup>3</sup> have been introduced, and have already found huge practical application. In an attempt to reduce the high attrition rate, therefore medicinal chemists are currently looking for novel 3D-shaped building blocks with high fraction of Fsp<sup>3</sup>-hybridized carbons.<sup>4,5</sup>

Recently, 3-azaspiro[3.3]alkanes were introduced as surrogates for the common 6-membered aliphatic heterocycles



Figure 1. 3-Azaspiro[4.3]alkanes in drug discovery.

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### **Results and Discussion**

**Design.** Modern medicinal chemistry requires novel molecular entities to be synthesized from inexpensive and readily available starting materials in only several steps.<sup>10</sup> It correlates well with the recently proposed guidelines for the *"ideal synthesis:"* a synthetic target must be *"prepared from readily available, inexpensive starting materials in one simple, safe, environmentally acceptable and resource effective operation that proceeds quickly and in quantitative yield."<sup>11</sup>* 

In a search for a robust method towards novel spirocycles, we turned our attention to the well-elaborated [3+2]-cycloaddition of azomethine ylide generated from reagent 112 with electrondeficient alkenes.<sup>13-16</sup> This method has been already used to prepare several cyclohexane annelated pyrrolidines.<sup>17</sup> At the same time, the smallest and most interesting four-memberedring annelated for unclear reasons remained mostly in the shadow so far.<sup>18</sup> Literature search revealed only one example in a patent by Roche chemists: Nitro-substituted alkene 2 reacted with reagent 1 towards the needed spirocyclic product 2a (Scheme 1).18 No detailed experimental procedures and physicochemical/spectral characterization was provided in the patent, however. Nevertheless, inspired by this report we decided to apply this idea for the similar transformation on the known ethoxycarbonyl-substituted alkene 3. We envisioned that similar alkenes can be easily synthesized in one step from available inexpensive four-membered ketones by Horner-Emmons-Wadsworth reaction. At the same time, we were very much concerned on the key [3+2]-cycloaddition of alkene 3, because CO<sub>2</sub>Et group is significantly less electron-withdrawing than NO<sub>2</sub>, and more bulky.

Very recently, Juhl reported a similar study.<sup>19</sup>



Scheme 1. Planning the synthesis of spirocycle 3.

**Validation**. We tested the model transformation on the reactive 3-oxetanone (Scheme 2). The alkene **3** with EWG =  $CO_2Et$  was synthesized by *Horner-Emmons-Wadsworth* reaction following the literature procedure.<sup>6</sup> For *in situ* generation of the azomethine ylide from  $1^{12}$  we used two methods: *cat.* TFA in ethyl acetate at room temperature (A);<sup>14a</sup> and *cat.* LiF in acetonitrile under heating (B).<sup>12,14b,c</sup> In fact, both methods worked well, and the desired product **3a** was obtained in 87-89% yield after purification. The synthesis was easily scaled up to obtain 100 g of **3a** in one synthesis run.



Scheme 2. Validation of the procedure.

**Reaction scope**. Having a working procedure in hand, we next studied the scope and limitations of the second step – [3+2]-cycloaddition. First, we used only the alkoxycarbonyl-substituted systems to stepwise reveal the limitations of variation of the four-membered rings in the alkenes **3-8** (Table 1). In fact, all of them – cyclobutanone, azetidinone, and thienone-derived alkenes gave the desired spirocyclic products in excellent yields. In general, method B gave slightly better yields. Indeed all the obtained products **3a-8a** were racemic, but using the chiral version of the reagent **1** allowed to easily introduce chiral auxiliary into the target core (**3b**) making possible obtaining the optically pure compounds by separating the corresponding diastereomers. Spirocycle **8a** was obtained as an inseparable mixture of two diastereomers.

Next, we changed H-substituent to F-atom while keeping the same EWG (CO<sub>2</sub>Alk), and a varied again the cyclic ketones (alkenes **9-12**). Fluorinated pyrrolidines **9a-12a**<sup>20</sup> were obtained in excellent yields of 71-91%.

Finally, we varied the EWGs: while the substrates with CO<sub>2</sub>Et-(2-12), CN- (15-17), CON (13), COMe (14), NO<sub>2</sub> (2), and SO<sub>2</sub>R-(18-20) smoothly gave the needed pyrrolidines 2a-20a. The PO<sub>3</sub>Me<sub>2</sub>-substituted alkene 21 failed to react presumably due to the large bulk.





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<sup>a</sup>Reagent 1, TFA, EtOAc, rt; <sup>b</sup>Reagent 1, LiF, CH<sub>3</sub>CN, 60 °C; <sup>c</sup>mixture of diastereomers (2/1). dmixture of diastereomers (3/1).

Synthesis of building blocks. Having developed a powerful tool towards the spirocyclic structures, we wanted next to synthesize the corresponding appropriately Nprotected building blocks ready for the direct use in drug discovery projects.



building blocks with two points of diversity were prepared. Reduction of nitriles 17a with LiAlH<sub>4</sub> (22) followed by N-Boc protection, and N-benzyl hydrogenation gave

Two points of diversity. First, several

the N-monoprotected spirocyclic diamine 23 (Scheme 3).



Scheme 3. Synthesis of N-Boc protected diamine 23.

Removal of the N-Bn group in pyrrolidine 9a by hydrogenation over Pd/C (24), followed by N-Boc protection and subsequent basic hydrolysis of the ester group gave the N-protected amino acid 25. Analogously, amino acids 26, 27, 29 and amine 28 were easily synthesized (Scheme 4).



Scheme 4. Synthesis of N-protected amino acids 25-27, 29 and amine 28.

Diversely substituted oxetane-containing building blocks aldehydes, ketones, esters, amides and amines - were also synthesized following standard chemical transformations from the esters 3a (Scheme 5).



Scheme 5. Synthesis of oxetane-containing building blocks.

Three points of diversity. Next, we synthesized several representative building blocks having three points of diversity. Having developed a powerful tool towards the spirocyclic structures, we wanted to synthesize the corresponding appropriately Nprotected spirocyclic multifunctional building blocks with three points of diversity.



First, standard transformations of functional groups in **8a** easily afforded amino acids **40-42** and the diamine **43** (Scheme 6).



Scheme 6. Synthesis of spirocyclic amino acids  $40\mathchar`-42$  and diamine 43 with three points of diversity.

Next, Pd-catalyzed hydrogenative removal of the N-benzyl group in pyrrolidine **5a** followed by N-Cbz protection gave compound **44**. Alkaline hydrolysis of the ester group furnished the diamino acid **45** (Scheme 7).



Scheme 7. Synthesis of the spirocyclic diamino acid  ${\bf 45}$  with three diversity points.

**Optically active building blocks**. Indeed, all above mentioned compounds were synthesized as racemic mixtures. Therefore, given the need of drug discovery, we also performed several representative syntheses of the target spirocyclic scaffolds as pure enantiomers.

First, racemic compound **3a** was separated on chiral HPLC (Scheme 8a). The optically pure compounds (R)-**33** and (S)-**46**, in turn, were obtained by enzymatic resolution of racemic alcohol **33** (Scheme 8b).



Scheme 8. Synthesis of optically active oxetane-containing building blocks: a) separation by chiral HPLC; b) enzymatic resolution.

We additionally developed a novel synthetic approach to the enantiomerically pure diamine **50** – a component of the potent antibacterial agent DV-7751 (Scheme 9).<sup>21</sup> In that case, racemic acid **29** was resolved using an external chiral auxiliary. In fact, acid **29** was converted with *Evans* oxazolidinone<sup>22</sup> into diastereomeric amides **47** and **48** that were separated chromatographically. Removal of the chiral auxiliary in **47** – to give acid (*S*)-**29** (*X*-*Ray*)<sup>23</sup> – followed by Curtius degradation provided the needed N-Boc protected diamine (*S*)-**50**.

Removal of the N-Cbz group in (S)-29 afforded the amino acid (S)-49.



Scheme 9. Novel synthesis of optically active diamine (S)-50.

**Physico-chemical properties.** After the synthesis of the target spirocyclic building blocks, we determined their physicochemical characteristics. We first measured the experimental logD (pH = 10) values of the N-Bn protected amines **7a**, **3a** and compared data with the piperidine **51** and morpholine **52** derivatives (Table 2). Indeed, compounds **7a**, **3a** possess higher molecular weights compared to models **51**, **52**. On the other hand, spirocyclic compounds have recently been shown to have lower lipophilicity than the common sixmembered heterocycles due to the pyramidalization of the heteroatoms in the four-membered rings (*spiro effect*).<sup>6</sup>

Experimental data showed that the higher molecular weights override the *spiro effect* as both compounds **7a**, **3a** were slightly more lipophilic than **51**, **52**. However, while the transition from **51** to **3a** led to  $\Delta \log D = 0.3$ , the same replacement of **52** for **3a** gave the minimal  $\Delta \log D = 0.1$ . It seems that the strong *spiro effect* in model **3a** (pyramidalization of O-atom in oxetane) decreases its lipophilicity, while the same effect is absent in cyclobutane derivative **7a**. Spirocyclic compound **7a** had lower water solubility than that of model **51** due to the higher molecular weight. Similar to the previous study,<sup>6</sup> both spirocyclic models **7a**, **3a** were significantly more metabolically stable (CL<sub>int</sub>) than the

analogous six-membered piperidine (51) and morpholine (52) derivatives.

In short summary, spirocyclic modules **3a**, **7a** possessed appropriated ADME profiles for drug discovery: they were slightly more lipophilic and less water soluble, but significantly more metabolically stable than the analogous piperidine (**51**) and morpholine (**52**) cores.

Table 2. Experimental ADME-parameters.

	Compound	Spiro effect	LogD(10) <sup>a</sup>	Sol(7.4) <sup>c</sup>	$CL_{int}^{\ b}$
51	CO <sub>2</sub> Et	n.a.	2.6	7	n.d. <sup>d</sup>
7a	CO <sub>2</sub> Et	No	2.9	2	120
52	CO₂Et O N Ph	n.a.	2.1	>10	n.d. <sup>d</sup>
3a	CO <sub>2</sub> Et	Yes	2.2	>10	50

<sup>a</sup>Experimental n-octanol/water distribution coefficient (log) at pH 7.4; <sup>b</sup>Intrinsic clearance rate  $CL_{int}$  (mg/(min·µL)) measured in mouse liver microsomes; <sup>c</sup>Thermodynamic aqueous solubility in 50 mM phosphate buffer (pH 7.4). <sup>d</sup> Very fast decomposition.

### Conclusions

We have elaborated a two-step approach to spirocyclic building blocks on a multigram scale from common fourmembered cyclic ketones. The key reaction was a [3+2]cycloaddition between electron-deficient alkenes and an *in situ* generated N-benzyl azomethine ylide. Given the appropriate ADME profiles of the developed scaffolds, and their rapid synthesis, we believe that this efficient method will find practical application very soon in drug discovery within both academia and industry.

### **Experimental Section**

Measured melting points are uncorrected. Solvents were purified according to standard procedures. Column chromatography was performed using Kieselgel Merck 60 (230-400 mesh) as the stationary phase. <sup>1</sup>H-, <sup>19</sup>F-, <sup>13</sup>C-NMR spectra were recorded on at 500 or 400 MHz, 376 MHz and 125 or 101 MHz respectively. Chemical shifts are reported in ppm downfield from TMS (<sup>1</sup>H, <sup>13</sup>C) or CFCl<sub>3</sub> (<sup>19</sup>F) as internal standards. Mass spectra were recorded on an LC-MS instrument with chemical ionization (CI) or a GC-MS instrument with electron impact ionization (EI). LC-MS data were acquired on Agilent 1200 HPLC system equipped with DAD/ELSD/LCMS-6120 diodematrix and mass-selective detector, column: Poroshell 120 SBC18, 4.6 mm × 30 mm. Eluent, A, acetonitrilewater with 0.1% of FA (99: 1); B, water with 0.1% of FA. Optical rotations were measured on polarimeter in methanol using 1 dm cell; optical rotation values are given in 10<sup>-1</sup> deg cm<sup>2</sup> g<sup>-1</sup>; concentrations (M) are given in mmol L<sup>-1</sup>, wavelength 589 nm at 20 °C. The enantiomeric excess and retention time (t<sub>R</sub>) was determined for major signal by HPLCs: Daicel CHIRALPACK IA, 5 µm, 4.6 × 250 mm, Daicel CHIRALPACK IB, 5 µm,

4.6 x 250 mm, Daicel CHIRALPACK OJ-H, 5 µm, 4.6 x 250 mm, Daicel CHIRALPACK AS-H, 5µm, 4.6 x 250 mm chiral columns, injection volume 0.1 µL, eluent (hexane: 2-propanol). Solid compounds were recrystalized from acetonitrile unless other is specified.

General procedure for [3+2] cycloadditions in the presence of TFA (method A).

A 10% solution of the corresponding alkene (1.0 eq.) in ethyl acetate was cooled to 0 °C under argon. **1** (1.1 eq.) was added and then a 10% solution of trifluoroacetic acid (0.15 eq.) in ethyl acetate was added dropwise. Reaction mixture was stirred overnight. After completion of the reaction (indicated by NMR) the mixture was washed with cold 10% solution of K<sub>2</sub>CO<sub>3</sub> twice, saturated solution of CuSO<sub>4</sub> for three times, cold 10% solution of K<sub>2</sub>CO<sub>3</sub> twice and brine once. Organic phase was separated, dried over Na<sub>2</sub>SO<sub>4</sub>, evaporated under reduced pressure and purified by distillation or column chromatography.

General procedure for [3+2] cycloaddition in the presence of LiF (method B).

A 10% solution of the corresponding alkene (1.0 eq.), **1** (1.2 eq.) and LiF (usually 3.0 eq., for compound **13** – 4.0 eq.) in CH<sub>3</sub>CN was stirred at 60 °C for 24-72 hours. After completion of the reaction (indicated by NMR) the mixture was evaporated under reduced pressure, dissolved in ethyl acetate and washed with a cold 10% solution of K<sub>2</sub>CO<sub>3</sub> twice, saturated solution of CuSO<sub>4</sub> for three times, cold 10% solution of K<sub>2</sub>CO<sub>3</sub> twice and brine once. Organic phase was separated, dried over Na<sub>2</sub>SO<sub>4</sub>, evaporated under reduced pressure and purified by distillation or column chromatography.

#### 6-Benzyl-8-nitro-2-oxa-6-azaspiro[3.4]octane (2a)

Pale yellow oil. 10% (A), 19% (B) yield.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.48 – 7.17 (m, 5H, Ph), 5.14 (dd, *J* = 7.4, 4.6 Hz, 1H, C*H*NO<sub>2</sub>), 4.69 (d, *J* = 6.1 Hz, 1H, C*H*HO), 4.64 – 4.39 (m, 3H, CH*H*O, C*H*<sub>2</sub>O), 3.72 (s, 2H, PhC*H*<sub>2</sub>N), 3.36 (dd, *J* = 11.0, 7.4 Hz, 1H, NC*H*HCH), 3.27 (d, *J* = 9.3 Hz, 1H, NC*H*H), 3.08 – 2.87 (m, 2H, NCH*H*CH, NCH*H*).

 $^{13}\text{C}$  NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  137.80 (s, Ph, C), 128.52 (s, Ph, o-CH, m-CH), 127.48 (s, Ph, p-CH), 90.45 (s, CHNO<sub>2</sub>), 82.16 (s, CH<sub>2</sub>O), 75.21 (s, CH<sub>2</sub>O), 62.07 (s, CH<sub>2</sub>NPh), 59.01 (s, CH<sub>2</sub>N), 57.65 (s, CH<sub>2</sub>N), 49.00 (s, C).

#### MS (EI, *m/z*): 248 (M <sup>+</sup>).

Anal. calcd for  $C_{13}H_{16}N_2O_3{:}$  C, 62.89; H, 6.50; N, 11.28. Found: C, 62.57; H, 6.28; N, 11.34.

### 6-Benzyl-2-oxa-6-aza-spiro[3.4]octane-8-carboxylic acid ethyl ester (3a)

A 60g of ethyl oxetan-3-ylideneacetate (freshly distilled at 5.5 mbar/64-66 °C, 422.0 mmol, 1.0 eq.) in ethyl acetate (600 mL) was cooled to -5 °C – 0 °C under argon in three necked 2L flask.

Amine 1 (freshly distilled, 120mL, 469.0 mmol, 1.1 eq.) was added and then 10% solution of trifluoroacetic acid (4.9 mL, 63.6 mmol, 0.15 eq.) in ethyl acetate (50mL) was slowly added dropwise. Reaction mixture was warmed to room temperature and stirred overnight. After completion of the reaction (indicated by NMR, if the conversion was not complete, appropriate quantity of trifluoroacetic acid in ethyl acetate was slowly added at 0 °C under argon), reaction mixture was diluted with cold 10% aqueous solution of K<sub>2</sub>CO<sub>3</sub> (500mL), washed 10% aqueous solution of K<sub>2</sub>CO<sub>3</sub> (2×200mL), and brine (2×100mL). Organic phase was separated, dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated and distilled under reduced pressure with Vigreaux column (I = 150mm).

The fraction collected at 60  $^{\circ}$ C – 125  $^{\circ}$ C (0.5 mbar) was discarded. The system was cooled down and charged with new containers and condenser (this procedure is necessary!).

The fraction collected at 125  $^{\rm o}C$  – 129  $^{\rm o}C$  (0.5 mbar) to afford the title compound (98.7-101.0 g, 85.0-86.9% yield) as a colorless liquid.

<sup>1</sup>H NMR (400 MHz, DMSO)  $\delta$  7.37 – 7.20 (m, 5H, Ph), 4.59 (d, *J* = 5.8 Hz, 1H, CC*H*HO), 4.46 (d, *J* = 6.6 Hz, 1H, CC*H*HO), 4.36 (d, *J* = 5.8 Hz, 1H, CC*H*HO), 4.32 (d, *J* = 6.6 Hz, 1H, CCHHO), 4.13 (m, 2H, CH<sub>3</sub>CH<sub>2</sub>O), 3.60 (m, 2H, CH<sub>2</sub>Ph), 3.14 (dd, *J* = 8.4, 6.4 Hz, 1H), 3.03 (d, *J* = 9.0 Hz, 1H), 2.86 (t, *J* = 9.0 Hz, 1H), 2.72 (d, *J* = 9.0 Hz, 1H), 2.55 (m, 1H), 1.22 (t, 3H, *J* = 7.0 Hz, CH<sub>3</sub>).

 $^{13}\text{C}$  NMR (101 MHz, DMSO)  $\delta$  172.95 (s,  $CO_2\text{Et}$ ), 139.09 (s, Ph, C), 128.86 (s, Ph, CH), 128.67(s, Ph, CH), 127.37(s, Ph, CH), 82.45 (s, CCH\_2O), 77.35 (s, CCH\_2O), 64.20 (s), 60.76(s), 59.22(s), 56.05(s), 49.84(s), 47.82(s), 14.62 (s, CH\_3).

MS (EI, m/z): 275 (M+).

Anal. calcd for  $C_{16}H_{21}NO_3:$  C, 69.79; H, 7.69; N, 5.09. Found: C, 70.11; H, 7.41; N, 5.40.

### (S)-6-Benzyl-2-oxa-6-aza-spiro[3.4]octane-8-carboxylic acid ethyl ester ((S)-3a)

Colorless liquid. 99.9% ee,  $[\alpha]^{20}$ <sub>D</sub> =-6.9, retention time 19.92 min.

<sup>1</sup>H NMR (400 MHz, DMSO)  $\delta$  7.37 – 7.20 (m, 5H, Ph), 4.59 (d, *J* = 5.8 Hz, 1H, CC*H*HO), 4.46 (d, *J* = 6.6 Hz, 1H, CC*H*HO), 4.36 (d, *J* = 5.8 Hz, 1H, CC*H*HO), 4.32 (d, *J* = 6.6 Hz, 1H, CC*H*HO), 4.13 (m, 2H, CH<sub>3</sub>C*H*<sub>2</sub>O), 3.60 (m, 2H, CH<sub>2</sub>Ph), 3.14 (dd, *J* = 8.4, 6.4 Hz, 1H), 3.03 (d, *J* = 9.0 Hz, 1H), 2.86 (t, *J* = 8.9 Hz, 1H), 2.72 (d, *J* = 9.0 Hz, 1H), 2.55 (m, 1H), 1.22 (t, 3H, *J* = 7.0 Hz, CH<sub>3</sub>)

 $^{13}C$  NMR (101 MHz, DMSO)  $\delta$  172.95 (s,  $CO_2Et)$ , 139.09 (s, Ph, C), 128.86 (s, Ph, CH), 128.67(s, Ph, CH), 127.37(s, Ph, CH), 82.45 (s, CCH\_2O), 77.35 (s, CCH\_2O), 64.20 (s), 60.76(s), 59.22(s), 56.05(s), 49.84(s), 47.82(s), 14.62 (s, CH\_3).

MS (EI, *m/z*): 275 (M<sup>+</sup>).

Anal. calcd for  $C_{16}H_{21}NO_3$ : C, 69.79; H, 7.69; N, 5.09. Found: C, 69.56; H, 7.31; N, 5.37.

### (*R*)-6-Benzyl-2-oxa-6-aza-spiro[3.4]octane-8-carboxylic acid ethyl ester ((*R*)-3a)

Colourless liquid. 61.7% ee, retention time 23.32 min.

<sup>1</sup>H NMR (400 MHz, DMSO)  $\delta$  7.37 – 7.20 (m, 5H, Ph), 4.59 (d, J = 5.8 Hz, 1H, CC*H*HO), 4.46 (d, J = 6.6 Hz, 1H, CC*H*HO), 4.36 (d, J = 5.8 Hz, 1H, CC*H*HO), 4.32 (d, J = 6.6 Hz, 1H, CC*H*HO), 4.13 (m, 2H, CH<sub>3</sub>CH<sub>2</sub>O), 3.60 (m, 2H, CH<sub>2</sub>Ph), 3.14 (dd, J = 8.4, 6.4 Hz, 1H), 3.03 (d, J = 9.0 Hz, 1H), 2.86 (t, J = 8.9 Hz, 1H), 2.72 (d, J = 9.0 Hz, 1H), 2.55 (m, 1H), 1.22 (t, 3H, J = 7.0 Hz, CH<sub>3</sub>).

 $^{13}C$  NMR (101 MHz, DMSO)  $\delta$  172.95 (s,  $CO_2Et$ ), 139.09 (s, Ph, C), 128.86 (s, Ph, CH), 128.67(s, Ph, CH), 127.37(s, Ph, CH), 82.45 (s, CCH\_2O), 77.35 (s, CCH\_2O), 64.20 (s), 60.76(s), 59.22(s), 56.05(s), 49.84(s), 47.82(s), 14.62 (s, CH\_3).

MS (EI, m/z): 275 (M +).

Anal. calcd for  $C_{16}H_{21}NO_3$ : C, 69.79; H, 7.69; N, 5.09. Found: C, 69.48; H, 7.85; N, 5.28.

### Ethyl 6-((*R*)-1-phenylethyl)-2-oxa-6-azaspiro[3.4]octane-8carboxylate (3b)

Yellow oil. 39% (A), 46% (B) yield.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of both diastereomers  $\delta$  7.43 – 7.00 (m, 5H, Ph), 4.70 – 3.92 (m, 7H, 2xCH<sub>2</sub>O, CH<sub>3</sub>CH<sub>2</sub>O, NHCH<sub>3</sub>), 3.31 – 2.48 (m, 5H, CHCO<sub>2</sub>Et, 2xCH<sub>2</sub>N), 1.40 – 1.03 (m, 6H, 2xCH<sub>3</sub>).

 $^{13}\text{C}$  NMR (101 MHz, CDCl<sub>3</sub>) of both diastereomers  $\delta$  173.06 (s), 172.98 (s), 145.05 (s), 144.93 (s), 128.46 (s), 128.38 (s), 127.11 (s), 127.07 (s), 127.03 (s), 126.95 (s), 84.07 (s), 83.37 (s), 78.20 (s), 77.56 (s), 64.84 (s), 64.79 (s), 63.29 (s), 62.91 (s), 60.79 (s), 60.76 (s), 55.31 (s), 55.06 (s), 50.26 (s), 50.01 (s), 47.74 (s), 47.60 (s), 23.08 (s), 22.88 (s), 14.30 (s).

MS (EI, *m/z*): 289 (M <sup>+</sup>).

Anal. calcd for  $C_{17}H_{23}NO_3\!\!:$  C, 70.56; H, 8.01; N, 4.84. Found: C, 70.81; H, 8.19; N, 4.95.

# 6-Benzyl-2-thia-6-aza-spiro[3.4]octane-8-carboxylic acid ethyl ester (4a)

Pale yellow oil. B. p. 140 – 148 °C (0.5 mbar). Purified by column chromatography (Hex/MTBE (70%/30%). 66% (A), 83% (B) yield.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.28 (m, 5H, Ph), 4.36 – 4.07 (m, 2H, CH<sub>2</sub>CH<sub>3</sub>), 3.65 (s, 2H, CH<sub>2</sub>Ph), 3.51 (d, J = 8.9 Hz, 1H), 3.41 (d, J = 9.5 Hz, 1H), 3.16 (d, J = 8.9 Hz, 1H), 3.03 – 2.50 (m, 6H), 1.31 (t, J = 6.9 Hz, 3H, CH<sub>2</sub>CH<sub>3</sub>).

 $^{13}\text{C}$  NMR (101 MHz, DMSO)  $\delta$  172.50 (s, CO<sub>2</sub>Et), 139.26 (s, Ph, C), 128.84 (s, Ph, CH), 128.70 (s, Ph, CH), 127.37 (s, Ph, CH), 66.00 (s), 60.79 (s), 59.20 (s), 55.25 (s), 53.08 (s), 52.74 (s), 37.10 (s), 33.62 (s), 14.68 (s, CH<sub>3</sub>).

#### MS (EI, m/z): 291 (M+).

Anal. calcd for  $C_{16}H_{21}NO_2S;\,C,\,65.95;\,H,\,7.26;\,N,\,4.81.$  Found: C,  $65.72;\,H,\,7.43;\,N,\,4.53.$ 

### 6-Benzyl-2,2-dioxo-2-thia-6-aza-spiro[3.4]octane-8-carboxylic acid ethyl ester (5a)

Brown solid. M. p. 65 - 68 °C. 87% (A), 90% (B) yield.

<sup>1</sup>H NMR (400 MHz, DMSO) δ 7.29 (m, 5H, Ph), 4.36 (d, J = 13.5 Hz, 1H), 4.26 – 4.03 (m, 4H), 3.97 (dd, J = 3.1, 13.8 Hz, 1H), 3.69 (d, J = 13.2 Hz, 1H, CHHPh), 3.65 (d, J = 13.2 Hz, 1H, CHHPh), 3.3 (m, 1H), 2.84 (m, 4H), 1.22 (t, J = 7.1 Hz, 3H, CH<sub>3</sub>).

 $^{13}\text{C}$  NMR (126 MHz, DMSO)  $\delta$  171.85 (s, CO<sub>2</sub>Et), 138.56 (s, Ph, C), 128.45 (s, Ph, CH), 128.33 (s, Ph, CH), 127.06 (s, Ph, CH), 73.64 (s, CH<sub>2</sub>SO<sub>2</sub>), 70.35 (s, CH<sub>2</sub>SO<sub>2</sub>), 63.94 (s), 60.79 (s), 58.45 (s), 54.43 (s), 49.76 (s), 33.58 (s, C), 14.04 (s, CH<sub>2</sub>CH<sub>3</sub>).

MS (EI, *m/z*): 323 (M <sup>+</sup>).

Anal. calcd for  $C_{16}H_{21}NO4S;\,C,\,59.42;\,H,\,6.55;\,N,\,4.33.$  Found: C, 59.22; H, 6.28; N, 4.58.

### 6-Benzyl-2,6-diaza-spiro[3.4]octane-2,8-dicarboxylic acid 2-tert-butyl ester 8-methyl ester (6a)

Colorless oil. Purified by column chromatography (Hex/MTBE (40%/60%). 89% (A), 93% (B) yield.

<sup>1</sup>H NMR (500 MHz, DMSO) δ 7.33 – 7.22 (m, 5H, Ph), 3.92 (d, J = 8.5 Hz, 1H CHHNBoc), 3.84 – 3.77 (m, 2H, 2xCHHNBoc), 3.71 (m, 4H, CHHNBoc, OMe), 3.62 (m, 2H, CH<sub>2</sub>Ph), 3.10 – 3.00 (m, 2H), 2.93 (d, J = 9.2 Hz, 1H), 2.79 – 2.71 (m, 1H), 2.67 (d, J = 9.2 Hz, 1H), 1.41 (s, 9H, Boc).

 $^{13}\text{C}$  NMR (126 MHz, DMSO)  $\delta$  172.91 (CO2Me), 155.76 (s, CO2'Bu), 138.11 (s, Ph, C), 128.15 (s, Ph, CH), 127.93(s, Ph, CH), 126.73(s, Ph, CH), 79.06 (s, C(CH3)), 64.13 (s), 61.36 (s), 59.17 (s), 56.01 (s), 55.77 (s), 51.50 (s), 50.46 (s), 41.91 (s), 27.96 (s, C(CH3)).

MS (CI, m/z): 361 (M+H+).

Anal. calcd for  $C_{20}H_{28}N_2O_4:$  C, 66.64; H, 7.83; N, 7.77. Found: C, 66.32; H, 8.17; N, 7.41.

6-Benzyl-6-aza-spiro[3.4]octane-8-carboxylic acid ethyl ester (7a)

Colorless oil. B. p. 115 - 120 °C (1 mbar). 64% (A), 85% (B) yield.

<sup>1</sup>H NMR (400 MHz, DMSO) δ 7.42 – 7.15 (m, 5H, Ph), 4.08 (m, 2H, CH<sub>2</sub>CH<sub>3</sub>), 3.58 (d, 1H, J = 13.3 Hz, CH<sub>H</sub>Ph), 3.53 (d, 1H, J = 13.3 Hz, CH<sub>H</sub>Ph), 2.83 – 2.71 (m, 3H), 2.71 – 2.58 (m, 1H), 2.50 (d, 1H, J = 8.3 Hz), 2.08 (m, 1H), 1.92 (m, 2H), 1.85 – 1.56 (m, 3H), 1.20 (t, J = 7.1 Hz, 3H, CH<sub>3</sub>).

 $^{13}C$  NMR (101 MHz, DMSO)  $\delta$  173.31 (s, CO2Et), 139.56 (s, Ph, C), 128.73 (s, Ph, CH), 128.57 (s, Ph, CH), 127.19 (s, Ph, CH), 66.01 (s, PhCH2), 60.28 (s), 59.70 (s), 55.95 (s), 52.87 (s), 48.25 (s), 34.76 (s), 29.70 (s), 16.87 (s), 14.70 (s).

MS (EI, *m/z*): 273 (M <sup>+</sup>).

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Anal. calcd for  $C_{17}H_{23}NO_2:$  C, 74.69; H, 8.48; N, 5.12. Found: C, 74.92; H, 8.84; N, 5.45.

#### 2-(tert-butyl) 8-methyl 6-benzyl-6-azaspiro[3.4]octane-2,8dicarboxylate (8a)

Colourless oil. 69% (A), 83% (B) yield.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of both diastereomers  $\delta$  7.45 – 7.11 (m, 5H, Ph), 3.78 – 3.44 (m, 5H), 3.08 – 1.95 (m, 10H), 1.41, 1.39 (2xs, 9H, Boc).

 $^{13}\text{C}$  NMR (126 MHz, CDCl<sub>3</sub>) of both diastereomers  $\bar{\mathrm{o}}$  174.74 (s), 173.98 (s), 173.87 (s), 138.93 (s), 138.82 (s), 128.63 (s), 128.58 (s), 128.25 (s), 128.21 (s), 126.97 (s), 126.93 (s), 80.09 (s), 79.99 (s), 66.81 (s), 65.24 (s), 59.90 (s), 59.81 (s), 56.24 (s), 55.93 (s), 53.25 (s), 52.89 (s), 51.56 (s), 51.50 (s), 44.70 (s), 44.09 (s), 38.33 (s), 38.17 (s), 34.54 (s), 33.73 (s), 32.89 (s), 32.25 (s), 28.03 (s), 27.98 (s).

MS (CI, *m/z*): 360 (M+H<sup>+</sup>).

Anal. calcd for  $C_{21}H_{29}NO_4$ : C, 70.17; H, 8.13; N, 3.90. Found: C, 70.33; H, 8.02; N, 3.67.

### 6-Benzyl-8-fluoro-2-oxa-6-aza-spiro[3.4]octane-8-carboxylic acid ethyl ester (9a)

Colorless oil. B. p. 122 – 125°C (0.5 mbar). 71% (A), 86% (B) yield.

<sup>1</sup>H NMR (400 MHz, DMSO) δ 7.31 (m, 5H, Ph), 4.74 (d, J = 6.2 Hz, 1H, CHHO), 4.31 (m, 5H, CHHO, CH<sub>2</sub>O, CH<sub>2</sub>CH<sub>3</sub>), 3.64 (s, 2H, CH<sub>2</sub>Ph), 3.21 (d, J = 9.3 Hz, 1H, CHHN), 3.12 – 2.78 (m, 3H, CHHN, CH<sub>2</sub>N), 1.25 (t, J = 7.1 Hz, 3H, CH<sub>3</sub>).

<sup>13</sup>C NMR (126 MHz, DMSO) δ 168.45 (d,  $\mathcal{J}^2(CF) = 29.1$  Hz,  $CO_2Et$ ), 137.99 (s, Ph, C), 128.49 (s, Ph, CH), 128.35 (s, Ph, CH), 127.14 (s, Ph, CH), 99.44 (d,  $J^1(CF) = 198$  Hz, CF), 75.65 (d,  $J^3(CF) = 6.1$  Hz, CH<sub>2</sub>O), 74.58 (d,  $J^3(CF) = 17.9$  Hz, CH<sub>2</sub>O), 62.96 (s), 62.16 (d,  $\mathscr{I}(CF) = 24.5$  Hz, CH<sub>2</sub>CF), 61.95 (s), 58.28 (s), 51.61 (d,  $\mathscr{I}(CF) = 22.5$  Hz, CCF), 14.01 (s, CH<sub>3</sub>).

<sup>19</sup>F NMR (376 MHz, DMSO) δ -158.20 (t, *J*<sup>3</sup>(FH) = 26.1 Hz).

MS (EI, *m/z*): 293 (M<sup>+</sup>).

Anal. calcd for  $C_{16}H_{20}FNO_3:$  C, 65.51; H, 6.87; N, 4.78. Found: C, 65.84; H, 7.07; N, 5.03.

### 6-Benzyl-8-fluoro-2-thia-6-aza-spiro[3.4]octane-8-carboxylic acid ethyl ester (10a)

Colorless oil. B. p. 132 - 135 °C (0.5 mbar). 87% (A), 88% (B) yield.

<sup>1</sup>H NMR (400 MHz, DMSO)  $\delta$  7.44 – 7.13 (m, 5H, Ph), 4.27 (m, 2H, CH<sub>2</sub>CH<sub>3</sub>), 3.77 – 3.58 (m, 2H, CH<sub>2</sub>Ph), 3.53 (d, *J* = 9.5 Hz, 1H), 3.29 – 3.13 (m, 2H), 3.04 (m, 2H), 2.96 – 2.71 (m, 3H), 1.27 (t, *J* = 7.1 Hz, 3H, CH<sub>2</sub>CH<sub>3</sub>).

 $^{13}\text{C}$  NMR (126 MHz, DMSO)  $\delta$  168.54 (d,  $\mathscr{I}(\text{CF})$  = 28.1 Hz,  $CO_2\text{Et}),$  138.75 (s, Ph, C), 128.97 (s, Ph, CH), 128.87 (s, Ph, CH), 127.63 (s, Ph, CH), 100.36 (d,  $\mathcal{J}^1(\text{CF})$  = 197.1 Hz, CF), 64.84 (s), 62.49 (s), 62.00 (d,

 $\mathcal{J}^{2}(\text{CF})$  = 24.4 Hz), 58.89 (s), 56.11 (d,  $\mathcal{J}^{2}(\text{CF})$  = 23.0 Hz), 32.39 (d,  $\mathcal{J}^{3}(\text{CF})$  = 5.0 Hz), 29.66 (d,  $\mathcal{J}^{3}(\text{CF})$  = 14.2 Hz), 14.56 (s, CH<sub>3</sub>).

<sup>19</sup>F NMR (376 MHz, DMSO)  $\delta$  -158.36 (t, *J* = 28.4 Hz).

MS (EI, m/z): 309 (M +).

Anal. calcd for  $C_{16}H_{20}FNO_2S;$  C, 62.11; H, 6.52; N, 4.53. Found: C, 61.88; H, 6.84; N, 4.22.

### 6-Benzyl-8-fluoro-2,6-diaza-spiro[3.4]octane-2,8-dicarboxylic acid 2-tert-butyl ester 8-ethyl ester (11a)

Colorless oil. Purified by column chromatography (Hex/MTBE (75%/25%). 89% (A), 91% (B) yield.

<sup>1</sup>H NMR (400 MHz, DMSO) δ 7.46 – 7.14 (m, 5H, Ph), 4.25 (m, 2H, CH<sub>2</sub>CH<sub>3</sub>), 4.03 (d, J = 8.5 Hz, 1H), 3.65 (m, 5H), 3.21 (dd, J = 27.5, 11.8 Hz, 1H, CHHCF), 2.93 (m, 3H), 1.29 (s, 9H, Boc), 1.23 (t, J = 7.0 Hz, 3H, CH<sub>3</sub>).

<sup>13</sup>C NMR (126 MHz, DMSO) δ 168.06 (d,  $J^2$ (CF) = 28.5 Hz, CO<sub>2</sub>Et), 155.49 (s, CO<sub>2</sub>'Bu), 138.08 (s, Ph, C), 128.41 (s, Ph, CH), 128.32 (s, Ph, CH), 127.10 (s, Ph, CH), 100.03 (d, J'(CF) = 196.7 Hz, CF), 78.93 (s, C(CH<sub>3</sub>)<sub>3</sub>), 62.60 (s), 61.97 (s), 61.55 (d,  $J^2$ (CF) = 24.4 Hz, CH<sub>2</sub>CF), 58.33 (s), 55.51 (s), 52.73 (s), 46.06 (d,  $J^2$ (CF) = 22.7 Hz, CCF), 27.98 (s, C(CH<sub>3</sub>)<sub>3</sub>), 13.94 (s, CH<sub>2</sub>CH<sub>3</sub>).

<sup>19</sup>F NMR (376 MHz, DMSO)  $\delta$  -155.71 (t,  $J^3$ (FH) = 27.5 Hz).

MS (CI, *m/z*): 393 (M+H<sup>+</sup>).

Anal. calcd for  $C_{21}H_{29}FN_2O_4{:}$  C, 64.27; H, 7.45; N, 7.14. Found: C, 64.60; H, 7.18; N, 7.36.

# 6-Benzyl-8-fluoro-6-aza-spiro[3.4]octane-8-carboxylic acid ethyl ester (12a)

Colorless oil. B. p. 112 – 118 °C (1 mbar). 84% (A), 87% (B) yield.

<sup>1</sup>H NMR (400 MHz, CDCl3) δ 7.28 (m, 5H, Ph), 4.27 (m, 2H, CH<sub>2</sub>CH<sub>3</sub>), 3.67 (d, 1H, J = 13.5 Hz, CHHPh), 3.62 (d, 1H, J = 13.5 Hz, CHHPh), 3.16 (dd, J = 26.1, 11.5 Hz, 1H, CHHCF), 3.01 (m, 2H), 2.70 (d, J = 8.8 Hz, 1H), 2.49 (m, 1H), 2.05 – 1.93 (m, 1H), 1.87 – 1.65 (m, 4H), 1.31 (t, J = 7.1 Hz, 3H, CH<sub>3</sub>).

<sup>13</sup>C NMR (126 MHz, DMSO) δ 169.15 (d,  $\mathscr{P}(CF) = 29.5$  Hz, CO<sub>2</sub>Et), 138.48 (s, Ph, C), 128.39 (s, Ph, CH), 128.29 (s, Ph, CH), 127.00 (s, Ph, CH), 100.81 (d, J'(CF) = 195 Hz, CF), 64.47 (s), 62.25 (d,  $\mathscr{P}(CF) = 25.5$ Hz, CH<sub>2</sub>CF), 61.38 (s), 58.73 (s), 51.37 (d,  $\mathscr{P}(CF) = 25.5$  Hz, CCF), 28.75 (d,  $J^{3}(CF) = 4.5$  Hz), 26.85 (d,  $J^{3}(CF) = 13.8$  Hz), 15.85 (s), 14.13 (s).

<sup>19</sup>F NMR (376 MHz, DMSO) δ -156.28 (t, *J*<sup>3</sup>(FH) = 26.1 Hz).

MS (EI, *m/z*): 291 (M<sup>+</sup>).

Anal. calcd for  $C_{17}H_{22}FNO_2:$  C, 70.08; H, 7.61; N, 4.81. Found: C, 69.83; H, 7.92; N, 5.06.

# 6-Benzyl-N-methoxy-N-methyl-2-oxa-6-azaspiro[3.4]octane-8-carboxamide (13a)

Pale yellow oil. 68% (A), 76% (B) yield.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.27 (m, 5H), 4.67 (d, J = 5.4 Hz, 1H), 4.58 (d, J = 7.0 Hz, 1H), 4.48 (m, 2H), 3.73 (s, 3H), 3.61 (s, Hz, 3H), 3.33 (d, J = 9.0 Hz, 1H), 3.27 – 3.08 (m, 4H), 2.63 (d, J = 8.9 Hz, 1H), 2.47 (t, J = 8.5 Hz, 1H).

 $^{13}\text{C}$  NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  173.89 (s, CO), 138.69 (s, Ph, C), 128.64 (s, Ph, CH), 128.28 (s, Ph, CH), 127.06 (s, Ph, CH), 85.43 (s), 77.39 (s), 64.92 (s), 61.57 (s), 59.68 (s), 57.54 (s), 48.34 (s), 46.61 (s), 32.04 (s).

MS (EI, *m/z*): 290 (M <sup>+</sup>).

Anal. calcd for  $C_{16}H_{22}N_2O_3:$  C, 66.18; H, 7.64; N, 9.65. Found: C, 66.37; H, 7.71; N, 9.43.

#### 1-(6-benzyl-2-oxa-6-azaspiro[3.4]oct-8-yl)ethanone (14a)

Yellow oil. B. p. 120-124 °C (0.5 mbar). 83% (A), 89% (B) yield.

<sup>1</sup>H NMR (500 MHz, DMSO)  $\delta$  7.29 (m, 5H, Ph), 4.60 (d, J = 5.7 Hz, 1H, CHHO), 4.44 (d, J = 6.7 Hz, 1H, CHHO), 4.38 (d, J = 5.7 Hz, 1H, CHHO), 4.33 (d, J = 6.7 Hz, 1H, CHHO), 3.58 (d, J = 13.2 Hz, 1H, PhCHHN), 3.55 (d, J = 13.2 Hz, 1H, PhCHHN), 3.40 – 3.27 (m, 2H), 3.00 (d, J = 9.0 Hz, 1H), 2.83 (t, J = 9.0 Hz, 1H), 2.68 (d, J = 9.0 Hz, 1H), 2.50 (s, 2H), 2.45 (dd, J = 9.3, 6.4 Hz, 1H), 2.20 (s, 3H, CH<sub>3</sub>).

 $^{13}\text{C}$  NMR (126 MHz, CDCl<sub>3</sub>)  $\bar{\text{o}}$  208.49 (s, CO), 139.20 (s, Ph, C), 128.80 (s, Ph, CH), 128.65 (s, Ph, CH), 127.33 (s, Ph, CH), 83.34 (s), 77.30 (s), 64.71 (s), 59.38 (s), 56.91 (s), 55.91 (s), 47.63 (s), 30.71 (s, CH\_3).

MS (EI, *m/z*): 245 (M<sup>+</sup>).

Anal. calcd for  $C_{15}H_{19}NO_2:$  C, 73.44; H, 7.81; N, 5.71. Found: C, 73.13; H, 7.52; N, 5.83.

#### 6-Benzyl-2-oxa-6-aza-spiro[3.4]octane-8-carbonitrile (15a)

Colorless oil. B. p. 135 - 145 °C (0.5 mbar). 81% (A), 87% (B) yield.

 $^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$  7.31 (m, 5H, Ph), 4.71 (d, J=6.5 Hz, 1H), 4.55 (m, 2H), 4.45 (d, J=6.2 Hz, 1H), 3.69 – 3.53 (m, 3H), 3.00 – 2.79 (m, 3H), 2.68 – 2.61 (m, 1H).

 $^{13}\text{C}$  NMR (126 MHz, DMSO)  $\delta$  138.13 (s, Ph, C), 128.51 (s, Ph, CH), 128.36 (s, Ph, CH), 127.14 (s, Ph, CH), 120.23 (s, CN), 80.68 (s), 78.13 (s), 62.54 (s), 58.15 (s), 56.11 (s), 46.58 (s), 35.98 (s).

MS (EI, *m/z*): 228 (M<sup>+</sup>).

Anal. calcd for  $C_{14}H_{16}N_2O$ : C, 73.66; H, 7.06; N, 12.27. Found: C, 73.91; H, 6.78; N, 12.59.

#### 6-Benzyl-8-cyano-2,6-diaza-spiro[3.4]octane-2-carboxylic acid tertbutyl ester (16a)

Colorless oil. Purified by column chromatography (Hex/MTBE (40%/60%). 75% (A), 80% (B) yield.

<sup>1</sup>H NMR (500 MHz, DMSO)  $\delta$  7.39 – 7.18 (m, 5H, Ph), 3.99 (d, J = 8.2 Hz, 1H, CC*H*HN), 3.87 (d, J = 8.2 Hz, 1H, CC*H*HN), 3.82 (d, J = 8.2 Hz, 1H, CC*H*HN), 3.74 (d, J = 8.2 Hz, 1H, CCH*H*N), 3.64 – 3.54 (m, 3H), 2.90 (t, J = 8.7 Hz, 1H), 2.82 – 2.73 (m, 2H), 2.67 (dd, J = 9.4, 5.8 Hz, 1H), 1.37 (s, 9H, Boc).

 $^{13}\text{C}$  NMR (126 MHz, DMSO)  $\delta$  155.56 (s, CO2'Bu), 138.21 (s, Ph, C), 128.46 (s, Ph, CH), 128.36 (s, Ph, CH), 127.12 (s, Ph, CH), 120.25 (s, CN), 78.91 (s, C(CH\_3)\_3), 62.90 (s), 59.83 (s), 58.16 (s), 57.12 (s), 56.01 (s), 41.11 (s), 36.51 (s), 28.07 (s, C(CH\_3)\_3).

MS (CI, *m/z*): 328 (M+H<sup>+</sup>).

Anal. calcd for  $C_{19}H_{25}N_3O_2$ : C, 69.70; H, 7.70; N, 12.83. Found: C, 70.01; H, 7.32; N, 12.60.

#### 6-Benzyl-6-aza-spiro[3.4]octane-8-carbonitrile (17a)

Colorless oil. B. p. 115 - 120 °C (1 mbar). 68% (A), 74% (B) yield.

 $^1H$  NMR (400 MHz, DMSO)  $\delta$  7.42 – 7.15 (m, 5H, Ph), 3.65 (m, 2H), 3.02 (m, 1H), 2.93 (d, 1H), 2.83 – 2.71 (d, 1H), 2.71 – 2.58 (m, 2H), 2.47 (m, 1H), 2.24 (s, 1H), 2.06 (m, 2H), 1.90 – 1.88 (m, 2H).

 $^{13}\text{C}$  NMR (101 MHz, DMSO)  $\delta$  138.53 (s, Ph, C), 128.69 (s, Ph, CH), 128.56 (s, Ph, CH), 127.33 (s, Ph, CH), 120.39 (s, CN), 65.62 (s), 59.62 (s), 56.87 (s), 47.14 (s), 39.30 (s), 34.80 (s), 31.16 (s), 16.64 (s, CH\_2(CH\_2)\_2).

MS (EI, *m/z*): 226 (M <sup>+</sup>).

Anal. calcd for  $C_{15}H_{18}N_2\!\!:$  C, 79.61; H, 8.02; N, 12.38. Found: C, 79.67; H, 8.32; N, 12.17.

### 6-Benzyl-8-methanesulfonyl-2-oxa-6-aza-spiro[3.4]octane (18a)

Pale yellow oil. Purified by column chromatography (CHCl<sub>3</sub>/CH<sub>3</sub>CN (75%/25%). 74% (A), 87% (B) yield.

<sup>1</sup>H NMR (500 MHz, DMSO+CCl<sub>4</sub>)  $\delta$  7.27 (m, 5H, Ph), 5.31 (d, *J* = 6.6 Hz, 1H), 4.66 (d, *J* = 5.4 Hz, 1H), 4.31 (m, 2H), 3.91 (d, *J* = 7.6 Hz, 1H), 3.63 (s, 2H, CH<sub>2</sub>Ph), 3.06 (m, 2H), 2.94 (s, 3H, SO<sub>2</sub>Me), 2.75 (d, *J* = 8.7 Hz, 1H), 2.65 (s, 1H).

 $^{13}\text{C}$  NMR (126 MHz, DMSO)  $\delta$  138.62 (s, Ph, C), 129.08 (s, Ph, CH), 128.87 (s, Ph, CH), 127.69 (s, Ph, CH), 83.22 (s), 75.54 (s), 65.73 (s), 65.25 (s), 58.99 (s), 54.83 (s), 46.71 (s), 41.34 (s).

MS (CI, *m/z*): 282 (M+H<sup>+</sup>).

Anal. calcd for  $C_{14}H_{19}NO_3S;\,C,\,59.76;\,H,\,6.81;\,N,\,4.98.$  Found: C, 59.98; H, 6.47; N, 5.29.

#### 6-Benzyl-8-(phenylsulfonyl)-2-oxa-6-azaspiro[3.4]octane (19a)

White crystals. M. p. 123°C. 46% (A), 61% (B) yield.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.86 (d, *J* = 7.5 Hz, 2H), 7.64 (t, *J* = 7.5 Hz, 1H), 7.55 (t, *J* = 7.5 Hz, 2H), 7.25 (m, 5H), 5.65 (d, *J* = 6.9 Hz, 1H), 4.71 (d, *J* = 5.6 Hz, 1H), 4.47 (d, *J* = 6.9 Hz, 1H), 4.40 (d, *J* = 5.6 Hz, 1H), 3.74 (t, *J* = 7.9 Hz, 1H), 3.60 (d, *J* = 12.9 Hz, 1H), 3.54 (d, *J* = 12.9 Hz, 1H), 3.35 (d, *J* = 9.1 Hz, 1H), 2.77 (m, 2H), 2.62 – 2.42 (m, 1H).

 $^{13}\text{C}$  NMR (126 MHz, CDCl<sub>3</sub>)  $\bar{\text{o}}$  139.16 (s), 138.00 (s), 134.06 (s), 129.46 (s), 128.49 (s), 128.43 (s), 128.17 (s), 127.32 (s), 84.42 (s), 75.59 (s), 67.29 (s), 64.74 (s), 59.13 (s), 55.31 (s), 47.25 (s).

#### MS (CI, m/z): 344 (M+H+).

Anal. calcd for  $C_{19}H_{21}NO_3S;\,C,\,66.45;\,H,\,6.16;\,N,\,4.08.$  Found: C,  $66.09;\,H,\,6.28;\,N,\,4.33.$ 

### 6-Benzyl-8-ethoxysulfonyl-2,6-diaza-spiro[3.4]octane-2-carboxylic acid tert-butyl ester (20a)

Brown oil. 63% (A), 79% (B) yield.

 $^{1}\text{H}$  NMR (500 MHz, DMSO)  $\delta$  7.26 (m, 5H, Ph), 4.40 (d, J = 8.3 Hz, 1H), 4.31 (m, 2H), 4.18 (s, 1H), 3.93 (d, J = 8.2 Hz, 1H), 3.62 (m, 4H), 3.17 – 3.08 (m, 1H), 2.95 (d, J = 9.1 Hz, 1H), 2.80 – 2.57 (m, 2H), 1.42 – 1.25 (m, 12H, Boc, CH<sub>2</sub>CH<sub>3</sub>).

 $^{13}\text{C}$  NMR (126 MHz, DMSO)  $\bar{\delta}$  156.17 (s, CO2<sup>I</sup>Bu), 138.63 (s, Ph, C), 129.03 (s, Ph, CH), 128.89 (s, Ph, CH), 127.68 (s, Ph, CH), 79.40 (s, C(CH<sub>3</sub>)<sub>3</sub>), 67.94 (s), 64.76 (s), 63.08 (s), 61.42 (s), 58.71 (s), 54.66 (s), 41.13 (s), 28.65 (s), 28.58 (s), 15.44 (s, CH<sub>2</sub>CH<sub>3</sub>).

MS (CI, m/z): 411 (M+H+).

Anal. calcd for  $C_{20}H_{30}N_2O_5S;\,C,\,58.51;\,H,\,7.37;\,N,\,6.82.$  Found: C, 58.84; H, 7.61; N, 6.58.

#### C-(6-Benzyl-6-aza-spiro[3.4]oct-8-yl)-methylamine (22)

Colorless oil. 79% yield.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.31 (s, 5H, Ph), 3.62 (d, J = 13.0 Hz, 1H, C/HPh), 3.57 (d, J = 13.0 Hz, 1H, CH/Ph), 3.06 – 2.85 (m, 2H), 2.80 (d, J = 9.0 Hz, 1H), 2.59 – 2.40 (m, 2H), 2.18 (m, 2H), 2.04 – 1.62 (m, 6H), 1.11 (s, 2H, NH<sub>2</sub>).

 $^{13}\text{C}$  NMR (101 MHz, DMSO)  $\bar{o}$  140.00 (s, Ph, C), 128.72 (s, Ph, CH), 128.52 (s, Ph, CH), 127.05 (s, Ph, CH), 67.52 (s), 60.46 (s), 59.00 (s), 49.84 (s), 47.40 (s), 43.63 (s), 35.51 (s), 28.26 (s), 17.61 (s, CH<sub>2</sub>(CH<sub>2</sub>)<sub>2</sub>).

MS (CI, m/z): 231 (M+H+).

Anal. calcd for  $C_{15}H_{22}N_2:$  C, 78.21; H, 9.63; N, 12.16. Found: C, 77.89; H, 9.87; N, 11.94.

### (6-Aza-spiro[3.4]oct-8-ylmethyl)-carbamic acid tert-butyl ester (23)

White solid. M. p. 73 - 75°C. 89% yield.

 $^1\text{H}$  NMR (500 MHz, DMSO)  $\delta$  6.83 (s, 1H, N*H*Boc), 3.21 – 3.01 (m, 1H), 3.01 – 2.55 (m, 5H), 2.44 (dd, J = 10.2, 5.3 Hz, 1H), 2.07 (m, 1H), 1.82 (m, 5H), 1.60 (m, 1H), 1.37 (s, 9H, Boc).

 $^{13}\text{C}$  NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  156.26 (s, CO<sub>2</sub>'Bu), 77.91 (s, C(CH<sub>3</sub>)<sub>3</sub>), 59.30 (s), 50.11 (s), 48.31 (s), 47.66 (s), 41.12 (s), 33.30 (s), 28.84 (s, C(CH<sub>3</sub>)<sub>3</sub>), 26.98 (s), 16.95 (s, CH<sub>2</sub>(CH<sub>2</sub>)<sub>2</sub>).

#### MS (CI, *m/z*): 241 (M+H<sup>+</sup>).

Anal. calcd for  $C_{13}H_{24}N_2O_2:$  C, 64.97; H, 10.07; N, 11.66. Found: C, 65.22; H, 9.84; N, 11.31.

### 8-Fluoro-2-oxa-6-aza-spiro[3.4]octane-8-carboxylic acid ethyl ester hydrochloride (24)

White solid. M. p. 135 - 137°C. 99% yield.

<sup>1</sup>H NMR (400 MHz, DMSO) δ 10.12 (s, 2H, NH<sub>2</sub>), 4.61 (d, J = 6.8 Hz, 1H, OCH*H*), 4.58 – 4.48 (m, 2H, 2x OC*H*H), 4.41 – 4.22 (m, 3H, OCH*H*, CH<sub>2</sub>CH<sub>3</sub>), 3.80 (d, J = 12.3 Hz, 1H, C*H*HNH<sub>2</sub>), 3.70 (m, 2H, t,  $J^{3}$ (HF) = 26.3 Hz, CH<sub>2</sub>CF), 3.50 (d, J = 12.3 Hz, 1H, CHHNH<sub>2</sub>), 1.25 (t, J = 7.1 Hz, 3H, CH<sub>2</sub>CH<sub>3</sub>).

<sup>13</sup>C NMR (101 MHz, DMSO) δ 165.91 (d,  $\mathscr{P}(CF) = 26.3$  Hz, CO<sub>2</sub>Et), 99.33 (d,  $J^{1}(CF) = 195.5$  Hz, CF), 75.91 (d,  $\mathscr{I}^{3}(CF) = 8.0$  Hz, CH<sub>2</sub>O), 71.43 (d,  $\mathscr{I}^{3}(CF) = 10.5$  Hz, CH<sub>2</sub>O), 63.28 (s, OCH<sub>2</sub>CH<sub>3</sub>), 51.77 (d,  $\mathscr{I}^{2}(CF) = 22.8$  Hz), 51.18 (s, CH<sub>2</sub>NH<sub>2</sub>), 51.16 (d,  $\mathscr{I}^{2}(CF) = 25.2$  Hz), 14.28 (s, CH<sub>3</sub>).

<sup>19</sup>F NMR (376 MHz, DMSO)  $\delta$  -162.74 (t,  $J^3$ (FH) = 26.3 Hz).

MS (CI, m/z): 204 (M-CI<sup>-</sup>).

Anal. calcd for C\_9H\_15ClFNO\_3: C, 45.10; H, 6.31; N, 5.84. Found: C, 44.88; H, 6.03; N, 6.11.

#### 8-Fluoro-2-oxa-6-aza-spiro[3.4]octane-6,8-dicarboxylic acid 6-tertbutyl ester (25)

White solid. M. p. 142 - 143°C. 90% yield.

<sup>1</sup>H NMR (400 MHz, DMSO) δ 10.94 (broad s, 1H, CO<sub>2</sub>*H*), 4.66 (d, J = 6.5 Hz, 1H, OC*H*H), 4.57 – 4.46 (m, 3H, OCH*H*, OCH<sub>2</sub>), 3.88 (d, J = 11.2 Hz, 1H, NC*H*H), 3.66 (m, 3H, NCH*H*, NC*H*2), 1.40 (s, 9H, Boc).

 $^{13}\text{C}$  NMR of both Boc-rotamers (126 MHz, DMSO)  $\delta$  168.21 (d,  $\mathcal{I}(\text{CF})$  = 25.6 Hz,  $\text{CO}_2\text{H})$ , 168.09 (d,  $\mathcal{I}(\text{CF})$  = 26.5 Hz,  $\text{CO}_2\text{H})$ , 153.34 (s,  $\text{CO}_2\text{Bu})$ , 153.19 (s,  $\text{CO}_2\text{^{15}Bu})$ , 98.74 (d,  $\mathcal{I}(\text{CF})$  = 192.9 Hz, CF), 97.97 (d,  $\mathcal{I}(\text{CF})$  = 192.6 Hz, CF), 79.29 (s), 76.39 (s), 72.20 (s), 53.38 (s), 53.03 (s), 52.66 (d,  $\mathcal{I}(\text{CF})$  = 24.5 Hz), 52.34 (d,  $\mathcal{I}(\text{CF})$  = 24.5 Hz), 50.24 (d,  $\mathcal{I}(\text{CF})$  = 22.4 Hz), 49.44 (d,  $\mathcal{I}(\text{CF})$  = 22.4 Hz), 28.02 (s, C(CH\_3)\_3).

<sup>19</sup>F NMR of both Boc-rotamers (376 MHz, DMSO) δ -165.70 (dd,  $J^3$ (FH) = 30.6, 21.5 Hz), -166.29 (dd,  $J^3$ (FH) = 29.4, 21.7 Hz).

MS (CI, m/z): 274 (M-H+).

Anal. calcd for  $C_{12}H_{18}FNO_5:$  C, 52.36; H, 6.59; N, 5.09. Found: C, 52.70; H, 6.24; N, 4.86.

# 2-Oxa-6-aza-spiro[3.4]octane-6,8-dicarboxylic acid 6-tert-butyl ester (26)

White solid. M. p. 90 - 93°C. 93% yield.

<sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O)  $\delta$  4.38 (m, 2H), 3.77 – 3.61 (m, 5H), 3.43 (d, *J* = 12.0 Hz, 1H), 3.26 (dd, *J* = 8.4, 2.5 Hz, 1H), 1.44 (m, 9H, Boc).

 $^{13}\text{C}$  NMR (101 MHz, D<sub>2</sub>O)  $\delta$  180.98 (s, CO<sub>2</sub>H), 155.64 (s, CO<sub>2</sub>¹Bu), 81.91 (s, C(CH<sub>3</sub>)<sub>3</sub>), 73.83 (s), 62.55 (s), 52.18 (s), 51.68 (s), 47.48 (s), 46.21 (s), 27.62 (s, C(CH<sub>3</sub>)<sub>3</sub>).

MS (CI, m/z): 256 (M-H+).

Anal. calcd for  $C_{12}H_{19}NO_5$ : C, 56.02; H, 7.44; N, 5.44. Found: C, 55.84; H, 7.76; N, 5.18.

### 2-Oxa-6-aza-spiro[3.4]octane-6,8-dicarboxylic acid 6-benzyl ester (27)

White solid. M. p. 117 - 120°C. 94% yield.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.32 (m, 5H, Ph), 5.09 (s, 2H, C*H*<sub>2</sub>Ph), 4.33 (d, J = 9.4 Hz, 1H), 4.16 (s, 1H), 3.90 (d, J = 11.6 Hz, 1H), 3.63 (m, 4H), 3.40 (d, J = 13.6 Hz, 1H), 3.09 (d, J = 7.0 Hz, 1H).

 $^{13}\text{C}$  NMR of both Cbz-rotamers (126 MHz, DMSO)  $\delta$  178.49 (s,  $CO_2\text{H}),$  154.20 (s,  $CO_2\text{Bn}),$  137.41 (s, Ph, C), 128.99 (s, Ph, CH), 128.42 (s, Ph, CH), 128.13 (s, Ph, CH), 73.42 (s), 66.73 (s), 63.14 (s), 53.44, 53.08 (2xs), 52.92, 52.04 (2xs), 48.51, 48.03 (2xs), 46.56, 45.65 (2xs).

MS (CI, *m/z*): 290 (M-H<sup>+</sup>).

Anal. calcd for  $C_{15}H_{17}NO_5\!\!:C,\,61.85;\,H,\,5.88;\,N,\,4.81.$  Found: C, 62.06; H, 6.12; N, 4.56.

### 8-Methanesulfonyl-2-oxa-6-aza-spiro[3.4]octane hydrochloride (28)

White solid. Decomposes above 165 °C. 95% yield.

<sup>1</sup>H NMR (400 MHz, DMSO) δ 7.91 (s, 2H, NH<sub>2</sub>), 5.20 (t, J = 9.2 Hz, 1H), 4.63 (t, J = 10.5 Hz, 1H), 4.57 – 4.38 (m, 3H), 3.73 (d, J = 11.7 Hz, 1H), 3.65 – 3.44 (m, 2H), 3.36 (t, J = 13.9 Hz, 1H), 3.16 (s, 3H, CH<sub>3</sub>).

 $^{13}\text{C}$  NMR (101 MHz, DMSO)  $\delta$  80.80 (s), 73.16 (s), 63.92 (s), 53.57 (s), 47.34 (s), 45.02 (s), 41.84 (s).

MS (CI, m/z): 192 (M-CI)

Anal. calcd for  $C_7H_{14}CINO_3S:$  C, 36.92; H, 6.20; N, 6.15. Found: C, 37.18; H, 6.53; N, 6.48.

#### 6-[(benzyloxy)carbonyl]-6-azaspiro[3.4]octane-8-carboxylic acid (29)

White crystals. M. p. 113°C. 92% yield.

 $^1\text{H}$  NMR (400 MHz, DMSO+CCl4)  $\delta$  12.55 (s, 1H, COO*H*), 7.34 (m, 5H, Ph), 5.06 (s, 2H, C*H*\_2Ph), 3.52 – 3.37 (m, 4H), 2.89 (m, 1H), 2.18 – 2.01 (m, 2H), 1.95 – 1.69 (m, 4H).

 $^{13}\text{C}$  NMR of both Cbz-rotamers (126 MHz, DMSO)  $\delta$  173.72 (s), 173.63 (s), 154.46 (s), 154.38 (s), 137.52 (s), 128.84 (s), 128.21 (s), 127.96 (s), 127.89 (s), 66.33 (s), 66.28 (s), 57.10 (s), 56.66 (s), 51.33 (s), 50.58 (s), 47.56 (s), 47.13 (s), 47.03 (s), 46.31 (s), 31.85 (s), 31.60 (s), 27.42 (s), 27.33 (s), 15.87 (s), 15.82 (s).

MS (CI, m/z): 288 (M-H+).

Anal. calcd for  $C_{16}H_{19}NO_4$ : C, 66.42; H, 6.62; N, 4.84. Found: C, 66.11; H, 6.42; N, 4.56.

### (8S)-6-[(benzyloxy)carbonyl]-6-azaspiro[3.4]octane-8-carboxylic acid ((S)-29)

A 10% solution of **47** (33.1 g, 73.9 mmol) in THF was cooled to 0 °C. Lithium hydroxide monohydrate (5.0 g, 118.2 mmol, 1.6 eq.), and then aqueous  $H_2O_2$  (35%, 25.4 mL, 295.6 mmol, 4 eq.) were added. The reaction mixture was stirred at room temperature for 2 h. A 10% solution of Na<sub>2</sub>SO<sub>3</sub> was added to quench the reaction. The reaction mixture was concentrated under reduced pressure,  $H_2O$  (200 mL) was added. The resulting aqueous solution was washed with DCM (5x200 mL), and covered with ethyl acetate (500 mL). The bilayer mixture of water and ethyl acetate was acidified with a 3N HCl solution to pH 2. The white

precipitate was observed during acidification. After separation of the organic layer, the resulting aqueous layer was extracted with ethyl acetate (5x200 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and then concentrated to yield the acid **(S)-29** (15.6 g, 73% yield).

White crystals. 97.1% ee,  $[\alpha]^{20}$  =-18.6, retention time 8.43 min.

 $^1H$  NMR (400 MHz, CDCl\_3)  $\delta$  11.42 (s, 1H, COO*H*), 7.55 – 7.10 (m, 5H, Ph), 5.14 (m, 2H), 3.80 – 3.42 (m, 4H), 2.90 (m, 1H), 2.20 (m, 2H), 1.92 (m, 4H).

<sup>13</sup>C NMR of both Cbz-rotamers (126 MHz, DMSO) 176.92 (s), 176.66 (s),
155.17 (s), 155.11 (s), 136.62 (s), 136.58 (s), 128.50 (s), 128.49 (s),
128.04 (s), 128.02 (s), 127.90 (s), 127.86 (s), 67.15 (s), 56.86 (s), 56.54 (s), 51.55 (s), 50.95 (s), 47.27 (s), 47.19 (s), 46.72 (s), 46.54 (s), 32.54 (s), 31.86 (s), 27.50 (s), 27.31 (s), 15.97 (s), 15.93 (s).

MS (CI, m/z): 288 (M-H+).

Anal. calcd for  $C_{16}H_{19}NO_4$ : C, 66.42; H, 6.62; N, 4.84. Found: C, 66.75; H, 6.91; N, 4.49.

#### 6-benzyl-8-(3-methyl-1,2,4-oxadiazol-5-yl)-2-oxa-6azaspiro[3.4]octane (30)

### Pale yellow oil. 65% yield.

<sup>1</sup>H NMR (400 MHz, DMSO)  $\delta$  7.51 – 7.02 (m, 5H, Ph), 4.67 (d, *J* = 6.1 Hz, 1H, OC*H*H), 4.46 (d, *J* = 6.1 Hz, 1H, OCH*H*), 4.29 (d, *J* = 6.7 Hz, 1H, OC*H*H), 4.07 (d, *J* = 6.7 Hz, 1H, OCH*H*), 3.89 (t, *J* = 7.5 Hz, 1H), 3.74 – 3.48 (m, 2H), 3.12 (d, *J* = 9.4 Hz, 1H), 3.06 (t, *J* = 8.9 Hz, 1H), 2.86 (d, *J* = 9.4 Hz, 1H), 2.75 (dd, *J* = 9.4, 7.0 Hz, 1H), 2.33 (s, 3H, CH<sub>3</sub>).

 $^{13}\text{C}$  NMR (101 MHz, DMSO)  $\delta$  179.51 (s, OCN), 167.32 (s, CCH<sub>3</sub>), 138.91 (s, Ph, C), 128.92 (s, Ph, CH), 128.72 (s, Ph, CH), 127.45 (s, Ph, CH), 81.97 (s, CH<sub>2</sub>O), 76.92 (s, CH<sub>2</sub>O), 63.87 (s), 59.13 (s), 57.09 (s), 48.78 (s), 42.86 (s), 11.60 (s, CH<sub>3</sub>).

#### MS (CI, *m/z*): 286 (M+H<sup>+</sup>).

Anal. calcd for  $C_{16}H_{19}N_3O_2:$  C, 67.35; H, 6.71; N, 14.73. Found: C, 67.72; H, 6.48; N, 14.95.

### 8-Hydroxymethyl-2-oxa-6-aza-spiro[3.4]octane-6-carboxylic acid benzyl ester (31)

Pale yellow oil. Purified by column chromatography (CHCl<sub>3</sub>/CH<sub>3</sub>CN (85%/15%). 70% yield.

 $^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$  7.36 (m, 5H, Ph), 5.05 (s, 2H, CH2Ph), 4.74 (m, 2H), 4.49 (d, J = 5.7 Hz, 1H), 4.42 (d, J = 5.7 Hz, 1H), 4.35 (d, J = 6.3 Hz, 1H), 3.72 – 3.49 (m, 3H), 3.49 – 3.33 (m, 2H), 3.22 (m, 1H), 2.35 (m, 1H).

<sup>13</sup>C NMR of both Cbz-rotamers (126 MHz, DMSO) δ 154.55 (s, COPh), 137.61 (s, Ph, C), 128.98 (s, Ph, CH), 128.35 (s, Ph, CH), 128.12, 128.07 (2xs, Ph, CH), 81.32, 81.06 (2xs), 75.40, 75.28 (2xs), 66.44 (s), 60.27 (s), 55.70, 55.18 (2xs), 48.46, 48.08 (2xs), 47.28 (s), 46.41, 45.62 (2xs).

MS (EI, *m/z)*: 277 (M <sup>+</sup>).

Anal. calcd for  $C_{15}H_{19}NO_4$ : C, 64.97; H, 6.91; N, 5.05. Found: C, 65.28; H, 6.59; N, 5.34.

# Benzyl 8-(fluoromethyl)-2-oxa-6-azaspiro[3.4]octane-6-carboxylate (32)

Colourless oil. 37% yield.

<sup>1</sup>H NMR (500 MHz, DMSO) δ 7.32 (m, 5H, Ph), 5.14 (s, 2H, CH<sub>2</sub>Ph), 4.85 (dd, J = 17.0, 6.2 Hz, 1H), 4.56 (m, 5H), 3.83 (d, J = 11.2 Hz, 1H), 3.71 (t, J = 12.8 Hz, 1H), 3.55 (m, 1H), 3.36 (m, 1H), 2.66 (d, J = 14.8 Hz, 1H).

 $^{13}\text{C}$  NMR of both Cbz-rotamers (126 MHz, DMSO)  $\delta$  154.40 (s), 154.36 (s), 137.45 (s), 128.88 (s), 128.30 (s), 128.08 (s), 83.14 (d,  $J^{\text{I}}(\text{CF})$  =

166.1 Hz), 80.81 (s), 80.56 (s), 75.36 (s), 75.25 (s), 66.56 (s), 55.46 (s), 54.99 (s), 47.41 (d,  $\mathscr{P}(\mathsf{CF})$  = 6.7 Hz), 47.05 (s), 47.03 (d,  $\mathscr{P}(\mathsf{CF})$  = 12.7 Hz), 46.22 (d,  $\mathscr{I}(\mathsf{CF})$  = 3.5 Hz), 44.33 (d,  $\mathscr{I}(\mathsf{CF})$  = 18.3 Hz), 43.53 (d,  $\mathscr{I}(\mathsf{CF})$  = 18.7 Hz).

<sup>19</sup>F NMR (376 MHz, DMSO) δ -225.29 (m).

MS (CI, *m/z*): 280 (M+H<sup>+</sup>).

Anal. calcd for  $C_{15}H_{18}FNO_3:$  C, 64.50; H, 6.50; N, 5.01. Found: C, 64.81; H, 6.75; N, 5.15.

8-Hydroxymethyl-2-oxa-6-aza-spiro[3.4]octane-6-carboxylic acid tert-butyl ester (33)

Colorless oil. Purified by column chromatography (Hex/MTBE (50%/50%). 56% yield.

<sup>1</sup>H NMR (400 MHz, DMSO) δ 4.73 (m, 2H), 4.50 (d, J = 5.8 Hz, 1H), 4.40 (s, 1H), 4.33 (d, J = 5.8 Hz, 1H), 3.54 (m, 3H), 3.41 (s, 1H), 3.30 – 3.19 (m, 1H), 3.13 (dd, J = 10.8, 5.0 Hz, 1H), 2.31 (s, 1H), 1.39 (s, 9H, Boc).

 $^{13}\text{C}$  NMR of both Boc-rotamers (101 MHz, DMSO)  $\delta$  154.06 (s, CO<sub>2</sub>'Bu), 81.20, 80.79 (2xs), 78.84 (s), 75.45, 75.31 (2xs), 60.19 (s), 55.42, 55.19 (2xs), 48.22, 47.83 (2xs), 47.12, 46.26 (2xs), 45.49 (2xs), 28.63 (s, C(CH<sub>3</sub>)<sub>3</sub>).

MS (EI, m/z): 243 (M+).

Anal. calcd for  $C_{12}H_{21}NO_4{:}$  C, 59.24; H, 8.70; N, 5.76. Found: C, 59.52; H, 8.98; N, 6.03.

# (8*R*)-8-hydroxymethyl-2-oxa-6-aza-spiro[3.4]octane-6-carboxylic acid tert-butyl ester ((*R*)-33)

Colorless oil. Purified by column chromatography (Hex/MTBE (67%/33%). 11% yield. 91.8% ee,  $[\alpha]^{20}_D$  =-23.6, retention time 10.79 min.

<sup>1</sup>H NMR (400 MHz, DMSO)  $\delta$  4.73 (m, 2H), 4.50 (d, *J* = 5.8 Hz, 1H), 4.40 (s, 1H), 4.33 (d, *J* = 5.8 Hz, 1H), 3.54 (m, 3H), 3.41 (s, 1H), 3.30 – 3.19 (m, 1H), 3.13 (dd, *J* = 10.8, 5.0 Hz, 1H), 2.31 (s, 1H), 1.39 (s, 9H, Boc).

 $^{13}\text{C}$  NMR of both Boc-rotamers (101 MHz, DMSO)  $\delta$  154.06 (s, CO<sub>2</sub>'Bu), 81.20, 80.79 (2xs), 78.84 (s), 75.45, 75.31 (2xs), 60.19 (s), 55.42, 55.19 (2xs), 48.22, 47.83 (2xs), 47.12, 46.26 (2xs), 45.49 (2xs), 28.63 (s, C(CH<sub>3</sub>)<sub>3</sub>).

MS (EI, m/z): 243 (M +).

Anal. calcd for  $C_{12}H_{21}NO_4{:}$  C, 59.24; H, 8.70; N, 5.76. Found: C, 59.61; H, 8.46; N, 5.39.

# 8-Formyl-2-oxa-6-aza-spiro[3.4]octane-6-carboxylic acid tert-butyl ester (34)

Colorless oil. Purified by column chromatography (Hex/MTBE (80%/20%). 81% yield.

 $^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$  9.75 (d, J = 6.5 Hz, 1H, C*H*O), 4.70 (d, J = 6.2 Hz, 1H), 4.62 (d, J = 5.5 Hz, 1H), 4.52 (s, 2H), 3.62 (m, 2H), 3.39 (m, 2H), 3.29 (m, 1H), 1.39 (s, 9H, Boc).

 $^{13}\text{C}$  NMR of both Boc-rotamers (101 MHz, DMSO)  $\delta$  202.32 (s, CHO), 153.89, 153.80 (2xs, CO2'Bu), 81.44, 81.14 (2xs), 79.20 (s), 75.43, 75.35 (2xs), 55.54, 54.85 (2xs), 54.79, 54.48 (2xs), 46.80, 46.02 (2xs), 44.55, 44.35 (2xs), 28.53 (s, C(CH\_3)\_3).

MS (EI, m/z): 241 (M+).

Anal. calcd for  $C_{12}H_{19}NO_4{:}$  C, 59.73; H, 7.94; N, 5.81. Found: C, 59.37; H, 8.16; N, 6.06.

8-(Methoxy-methyl-carbamoyl)-2-oxa-6-aza-spiro[3.4]octane-6carboxylic acid tert-butyl ester (35)



Colorless oil. Purified by column chromatography (CHCl<sub>3</sub>/CH<sub>3</sub>CN (70%/30%). 73% yield.

<sup>1</sup>H NMR of both Boc-rotamers (400 MHz, DMSO)  $\delta$  4.55 (d, J = 5.8 Hz, 1H, C*H*HO), 4.45 (m, 3H, C*H*<sub>2</sub>O, CH*H*O), 3.81 – 3.60 (m, 5H), 3.56 (t, J = 11.0 Hz, 1H), 3.44 (m, 1H), 3.34 (s, 1H), 3.12 (s, 3H, NC*H*<sub>3</sub>), 1.38 (s, 9H, Boc).

 $^{13}C$  NMR of both Boc-rotamers (126 MHz, DMSO)  $\delta$  172.34 (s, CONMe), 153.98, 153.82 (2xs, CO<sub>2</sub>'Bu), 82.33, 82.13 (2xs), 79.19 (s), 75.92 (s), 61.82 (s), 55.64, 55.39 (2xs), 48.58, 48.46 (2xs), 47.84, 47.03 (2xs), 46.28, 45.54 (2xs), 32.21 (s), 28.68 (s, C(CH\_3)\_3).

### MS (EI, *m/z*): 300 (M <sup>+</sup>).

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Anal. calcd for  $C_{14}H_{24}N_2O_5{:}$  C, 55.99; H, 8.05; N, 9.33. Found: C, 55.64; H, 8.32; N, 9.06.

# 8-Acetyl-2-oxa-6-aza-spiro[3.4]octane-6-carboxylic acid tert-butyl ester (36)

Colorless oil. Purified by column chromatography (Hex/MTBE (70%/30%). 77% yield.

<sup>1</sup>H NMR (400 MHz, DMSO) δ 4.64 – 4.34 (m, 4H, 2×C $H_2$ O), 3.62 (t, J = 11.1 Hz, 1H), 3.56 – 3.35 (m, 4H), 2.23 (s, 3H, COC $H_3$ ), 1.38 (s, 9H, Boc).

 $^{13}\text{C}$  NMR of both Boc-rotamers (101 MHz, DMSO)  $\delta$  208.17 (s, COMe), 153.90, 153.75 (2xs, CO2'Bu), 81.64, 81.26 (2xs), 79.16 (s), 76.17, 76.07 (2xs), 56.17, 55.47 (2xs), 55.28, 55.05 (2xs), 47.26, 46.35(2xs), 47.12 (s), 30.33, 30.21 (2xs), 28.56 (s, C(CH\_3)\_3).

MS (EI, *m/z*): 255 (M<sup>+</sup>).

Anal. calcd for  $C_{13}H_{21}NO_4$ : C, 61.16; H, 8.29; N, 5.49. Found: C, 60.88; H, 8.53; N, 5.19.

### 8-Benzoyl-2-oxa-6-aza-spiro[3.4]octane-6-carboxylic acid tert-butyl ester (37)

Pale yellow oil. Purified by column chromatography twice (CHCl<sub>3</sub>/CH<sub>3</sub>CN (80%/20%), Hex/MTBE (60%/40%). 69% yield.

<sup>1</sup>H NMR of both Boc-rotamers (500 MHz, DMSO)  $\delta$  8.03 (d, *J* = 7.5 Hz, 2H, o-C*H*), 7.69 (t, *J* = 7.5 Hz, 1H, *p*-C*H*), 7.57 (t, *J* = 7.5 Hz, 2H, *m*-C*H*), 4.84 – 4.37 (m, 5H), 3.76 (d, *J* = 9.7 Hz, 1H), 3.61 (m, 2H), 3.49 – 3.37 (m, 1H), 1.35 (2×s, 9H, Boc).

<sup>13</sup>C NMR of both Boc-rotamers (126 MHz, CDCl<sub>3</sub>) δ 199.80 (s, COPh), 154.06 (s, CO<sub>2</sub>'Bu), 136.31, 136.16 (2xs, Ph, C), 134.33 (s, Ph, CH), 129.52 (s, Ph, CH), 129.19 (s, Ph, CH), 82.28, 82.04 (2xs), 79.35 (s), 75.98 (s), 55.64, 55.48 (2xs), 51.25, 50.59 (2xs), 48.65 (s), 47.78, 46.97 (2xs), 28.65 (s, C(CH<sub>3</sub>)<sub>3</sub>).

MS (EI, *m/z*): 317 (M<sup>+</sup>).

Anal. calcd for  $C_{18}H_{23}NO_4{:}$  C, 68.12; H, 7.30; N, 4.41. Found: C, 68.43; H, 6.96; N, 4.18.

### 6-Benzyl-2-oxa-6-azaspiro[3.4]octane (38)

Colourless oil. B. p. 84°C (0.5 mbar). 78% yield.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.28 (m, 5H, Ph), 4.72 – 4.42 (m, 4H, 2xCH<sub>2</sub>O), 3.58 (s, 2H, CH<sub>2</sub>Ph), 2.80 (s, 2H, H-5), 2.53 (t, *J* = 6.7 Hz, 2H, H-7), 2.11 (t, *J* = 6.7 Hz, 2H, H-8).

 $^{13}\text{C}$  NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  138.84 (s, Ph, C), 128.69 (s, Ph, CH), 128.27 (s, Ph, CH), 127.02 (s, Ph, CH), 83.67 (s), 64.81 (s), 60.17 (s), 53.61 (s), 45.06 (s), 36.45 (s).

MS (EI, *m/z*): 203 (M<sup>+</sup>).

Anal. calcd for  $C_{13}H_{17}NO$ : C, 76.81; H, 8.43; N, 6.89. Found: C, 77.09; H, 8.62; N, 6.67.

#### 6-Benzyl 2-(tert-butyl) 8-methyl 6-azaspiro[3.4]octane-2,6,8tricarboxylate (39)

A 10% solution of **8a** (16.0 g, 44.4 mmol) in methanol, 5% palladium on charcoal and NH<sub>4</sub>Cl (2.5 g, 46.7 mmol) were mixed and stirred under H<sub>2</sub> (1 atm.) at room temperature overnight. Afterwards, the reaction mixture was filtered through celite and the solvent was evaporated under reduced pressure. The residue was recrystallized from CH<sub>3</sub>CN to give the hydrochloride of the corresponding amine (9.0 g, 29.4 mmol) that was dissolved in CH<sub>3</sub>CN (90 mL) and water (20 mL), the solution was cooled to 0°C. NaHCO<sub>3</sub> (3.7 g, 44.2 mmol) was added, reaction mixture was stirred for 0.5 h at 0°C and CbzOSu (8.1 g, 32.4 mmol) was added. Reaction mixture was stirred overnight, evaporated and extracted with ethyl acetate (3×20 mL). Organic layer was washed with 10% aqueous solution of NaHSO<sub>4</sub> (20 mL), twice, cold 10% aqueous solution of K<sub>2</sub>CO<sub>3</sub> (20 mL) twice and brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated under reduced pressure to give the product **39** (8.4 g, 56% yield).

#### Colorless oil.

 $^1\text{H}$  NMR of the mixture of diastereomers and Cbz-rotamers (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.31 (m, 5H, Ph), 5.12 (m, 2H, CH<sub>2</sub>Ph), 3.72 (m, 3H), 3.69 – 3.35 (m, 4H), 3.04 – 2.86 (m, 2H), 2.44 – 2.29 (m, 2H), 2.11 (m, 2H), 1.43 (s, 9H, Boc).

 $^{13}$ C NMR of the mixture of diastereomers and Cbz-rotamers (126 MHz, CDCl<sub>3</sub>)  $\delta$  174.21 (s), 174.00 (s), 173.79 (s), 173.74 (s), 171.99 (s), 171.88 (s), 171.75 (s), 154.70 (s), 154.65 (s), 154.47 (s), 136.72 (s), 128.44 (s), 128.41 (s), 127.96 (s), 127.90 (s), 127.84 (s), 127.82 (s), 127.79 (s), 80.43 (s), 80.36 (s), 80.31 (s), 66.87 (s), 66.85 (s), 66.80 (s), 57.52 (s), 57.04 (s), 56.54 (s), 56.18 (s), 51.92 (s), 51.89 (s), 51.86 (s), 51.83 (s), 51.65 (s), 43.65 (s), 43.65 (s), 43.65 (s), 42.51 (s), 42.53 (s), 35.14 (s), 34.93 (s), 34.52 (s), 33.33 (s), 32.90 (s), 30.82 (s), 30.70 (s), 30.66 (s), 30.45 (s), 27.98 (s).

#### MS (CI, m/z): 404 (M+H+).

Anal. calcd for  $C_{22}H_{29}NO_6\!\!:$  C, 65.49; H, 7.25; N, 3.47. Found: C, 65.17; H, 7.61; N, 3.32.

#### 6-((Benzyloxy)carbonyl)-8-(methoxycarbonyl)-6-azaspiro[3.4]octane-2-carboxylic acid (40)

A solution of **39** (3.0 g, 7.4 mmol) in DCM (10 mL) was cooled to 0°C and trifluoroacetic acid (2.5 g, 22.2 mmol, 3.0 eq.) was added. Reaction mixture was stirred at room temperature overnight and evaporated to afford the title compound (2.1 g, 81% yield).

White crystals. M. p. 116°C.

<sup>1</sup>H NMR of the mixture of diastereomers and Cbz-rotamers (500 MHz, CDCl<sub>3</sub>)  $\delta$  8.31 (s, 1H, COO*H*), 7.32 (m, 5H, Ph), 5.14 (m, 2H, C*H*<sub>2</sub>Ph), 3.90 – 3.34 (m, 7H), 3.12 (m, 1H), 2.95 (m, 1H), 2.70 – 1.91 (m, 4H).

 $^{13}\text{C}$  NMR of the mixture of diastereomers and Cbz-rotamers (126 MHz, CDCl<sub>3</sub>)  $\bar{0}$  179.66 (s), 179.38 (s), 179.31 (s), 171.94 (s), 171.81 (s), 171.78 (s), 171.65 (s), 154.96 (s), 154.89 (s), 154.77 (s), 136.48 (s), 128.51 (s), 128.48 (s), 128.09 (s), 128.04 (s), 127.95 (s), 127.89 (s), 127.87 (s), 67.18 (s), 67.16 (s), 67.10 (s), 57.46 (s), 57.11 (s), 56.53 (s), 56.22 (s), 52.08 (s), 52.05 (s), 52.01 (s), 51.98 (s), 51.56 (s), 51.11 (s), 50.95 (s), 50.40 (s), 47.10 (s), 46.63 (s), 43.59 (s), 43.36 (s), 42.94 (s), 42.62 (s), 34.89 (s), 34.81 (s), 34.24 (s), 30.64 (s), 30.44 (s).

MS (CI, m/z): 346 (M-H+).

Anal. calcd for  $C_{18}H_{21}NO_6{:}$  C, 62.24; H, 6.09; N, 4.03. Found: C, 62.51; H, 6.12; N, 4.25.

#### 6-Benzyl 8-methyl 2-((tert-butoxycarbonyl)amino)-6azaspiro[3.4]octane-6,8-dicarboxylate (41)

A mixture of **40** (1.6 g, 4.61 mmol, 1.0 eq.), DPPA (1.14 mL, 5.07 mmol, 1.1 eq.), triethylamine (0.77 mL, 5.53 mmol, 1.2 eq.) in tert-butanol (16 mL) was stirred overnight at 80°C. The reaction mixture was evaporated,

brine (20 mL) and ethyl acetate (20 mL) were added. The brine layer was extracted with ethyl acetate (3x20 mL). The combined organic layers were washed with cold 10% aqueous solution of K<sub>2</sub>CO<sub>3</sub> (2x30 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated under reduced pressure to give the product (1.1 g, 56% yield).

### Colorless oil.

<sup>1</sup>H NMR of the mixture of diastereomers and Cbz-rotamers (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.35 (s, 5H, Ph), 5.12 (s, 2H, CH<sub>2</sub>Ph), 4.70 (s, 1H), 4.10 (s, 1H), 3.79 – 3.35 (m, 7H), 2.95 – 2.79 (m, 1H), 2.55 – 2.25 (m, 2H), 2.14 – 1.83 (m, 2H), 1.42 (s, 9H).

 $^{13}$ C NMR of the mixture of diastereomers and Cbz-rotamers (126 MHz, CDCl<sub>3</sub>)  $\bar{0}$  172.29 (s), 172.16 (s), 171.81 (s), 171.70 (s), 154.90 (s), 154.68 (s), 154.62 (s), 154.56 (s), 154.47 (s), 136.63 (s), 128.46 (s), 128.43 (s), 127.94 (s), 127.81 (s), 79.28 (s), 66.87 (s), 57.78 (s), 57.30 (s), 56.25 (s), 55.83 (s), 51.88 (s), 51.83 (s), 51.18 (s), 50.60 (s), 49.82 (s), 47.49 (s), 47.02 (s), 46.55 (s), 41.66 (s), 41.24 (s), 40.91 (s), 40.54 (s), 40.47 (s), 40.16 (s), 39.94 (s), 36.79 (s), 36.14 (s), 35.92 (s), 28.36 (s).

MS (CI, m/z): 419 (M+H+).

Anal. calcd for  $C_{22}H_{30}N_2O_6:$  C, 63.14; H, 7.23; N, 6.69. Found: C, 62.97; H, 6.91; N, 6.75.

#### 6-((Benzyloxy)carbonyl)-2-(tert-butoxycarbonyl)-6azaspiro[3.4]octane-8-carboxylic acid (42)

A solution of **39** (6.0 g, 14.9 mmol) in a mixture of methanol (60 mL) and water (6 mL) was cooled to 0°C and treated with 10% aqueous sodium hydroxide solution (6.5 mL) and stirred overnight. The reaction mixture was evaporated, the residue was mixed with 10% aqueous NaHSO4 solution (20 mL) and extracted with ethyl acetate (3x20 mL). The combined organic layers were washed with brine (30 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated under reduced pressure to give the product (4.5 g, 78% yield).

#### Colorless oil.

 $^1\text{H}$  NMR of the mixture of diastereomers and Cbz-rotamers (400 MHz, DMSO)  $\delta$  12.57 (broad s, 1H, COO*H*), 7.35 (s, 5H, Ph), 5.06 (s, 2H, CH<sub>2</sub>Ph), 3.58 – 3.40 (m, 4H), 3.17 – 2.80 (m, 2H), 2.28 (m, 2H), 2.04 (m, 2H), 1.39 (s, 9H, Boc).

<sup>13</sup>C NMR of the mixture of diastereomers and Cbz-rotamers (126 MHz, CDCl<sub>3</sub>) δ 176.16 (s), 175.95 (s), 174.46 (s), 174.29 (s), 174.06 (s), 173.95 (s), 155.01 (s), 154.97 (s), 154.78 (s), 136.50 (s), 128.49 (s), 128.47 (s), 128.45 (s), 128.05 (s), 128.01 (s), 127.99 (s), 127.95 (s), 127.90 (s), 127.84 (s), 80.69 (s), 80.64 (s), 67.19 (s), 67.17 (s), 67.13 (s), 67.11 (s), 57.52 (s), 57.07 (s), 56.32 (s), 56.03 (s), 51.67 (s), 51.12 (s), 51.07 (s), 50.51 (s), 47.14 (s), 47.04 (s), 46.65 (s), 46.60 (s), 43.61 (s), 43.31 (s), 42.80 (s), 23.55 (s), 32.78 (s), 35.16 (s), 35.10 (s), 34.45 (s), 35.59 (s), 33.53 (s), 32.95 (s), 32.22 (s), 30.68 (s), 30.61 (s), 30.49 (s), 30.41 (s), 28.00 (s).

#### MS (CI, m/z): 388 (M-H+).

Anal. calcd for  $C_{21}H_{27}NO_6$ : C, 64.77; H, 6.99; N, 3.60. Found: C, 64.95; H, 6.93; N, 3.81.

# 8-Amino-6-((benzyloxy)carbonyl)-6-azaspiro[3.4]octane-2-carboxylic acid trifluoroacetate (43)

A mixture of **42** (4.3 g, 11.0 mmol, 1.0 eq.), DPPA (2.72 mL, 12.2 mmol, 1.1 eq.), triethylamine (1.85 mL, 13.3 mmol, 1.2 eq.), 2-thrimethylsilylethanol (15.8 mL, 10 eq., 110.4 mmol) in toluene (43 mL) was stirred overnight at 70°C. Reaction mixture was evaporated, brine (50 mL) and ethyl acetate (30 mL) were added. Brine layer was extracted with ethyl acetate (3×30 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated under reduced pressure. The residue was dissolved in DCM (50 mL), cooled to 0°C and treated with trifluoroacetic acid (6.3 g, 55.0 mmol, 5 eq.). Reaction mixture was stirred overnight (the completion was checked by NMR) at room temperature and evaporated to afford the product (2.1 g, 45% yield).

White crystals. M. p. 48-50°C.

 $^1\text{H}$  NMR of the mixture of diastereomers and Cbz-rotamers (400 MHz, DMSO)  $\delta$  11.93 (broad s, 1H, COO*H*), 8.20 (m, 3H, NH<sub>3</sub>), 7.36 (m, 5H, Ph), 5.06 (s, 2H, CH<sub>2</sub>Ph), 3.85 – 3.39 (m, 5H), 3.09 (s, 1H), 2.43 (s, 1H), 2.22 (s, 1H), 2.10 (s, 2H).

<sup>13</sup>C NMR of the mixture of diastereomers and Cbz-rotamers (101 MHz, DMSO) δ 176.17 (s), 176.13 (s), 159.16 (q, J = 32.8 Hz), 154.48 (s), 154.34 (s), 154.23 (s), 154.08 (s), 137.29 (s), 128.86 (s), 128.33 (s), 128.06 (s), 128.05 (s), 128.00 (s), 117.18 (q, J = 293 Hz), 48.60 (s), 43.50 (s), 42.96 (s), 42.72 (s), 42.15 (s), 35.88 (s), 35.80 (s), 35.11 (s), 34.98 (s), 31.78 (s), 31.73 (s), 31.65 (s), 31.60 (s), 27.80 (s), 26.97 (s), 26.94 (s).

<sup>19</sup>F NMR (376 MHz, DMSO) δ -74.58 (s).

MS (CI, *m/z*): 305 (M-CF<sub>3</sub>COO<sup>-</sup>).

Anal. calcd for  $C_{18}H_{21}F_{3}N_{2}O_{6}\!\!:$  C, 51.68; H, 5.06; N, 6.70. Found C, 51.53; H, 5.41; N, 6.48.

### 6-benzyl 2-(tert-butyl) 8-methyl 2,6-diazaspiro[3.4]octane-2,6,8-tricarboxylate (44)

A 10% solution of **6a** (3.60 g, 10.0 mmol) in ethanol, 5% palladium on charcoal (4.26 g, 2.0 mmol, 0.2eq.) and NH<sub>4</sub>Cl (0.56 g, 10.5 mmol, 1.05 eq.) were mixed and stirred under H<sub>2</sub> (1 atm.) at room temperature overnight. Afterwards, the reaction mixture was filtered through celite and the solvent was evaporated under reduced pressure. Then, THF (40 mL) and water (20 mL)were added and the formed solution was cooled to 0 °C. NaHCO<sub>3</sub> was added (3.36 g, 40 mmol, 4.0 eq.), reaction mixture was stirred for 0.5 h at 0 °C and CbzOSu (2.99 g, 12.0 mmol, 1.2 eq.) was added. Reaction mixture was stirred overnight, evaporated and extracted with ethyl acetate (3x20 mL). Organic layer was washed with 10% aqueous solution of NaHSO<sub>4</sub> (20 mL) twice, cold 10% aqueous solution of K<sub>2</sub>CO<sub>3</sub> (20 mL) twice and brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated under reduced pressure to give the product (4.00 g, 99% yield).

White crystals. M. p. 65°C.

 $^1\text{H}$  NMR of the mixture of Boc- and Cbz-rotamers (400 MHz, DMSO)  $\delta$  7.37 (m, 5H, Ph), 5.07 (s, 2H, CH<sub>2</sub>Ph), 3.92 (s, 1H), 3.78 (s, 3H), 3.64 (s, 3H), 3.55 (m, 4H), 2.54 (s, 1H), 1.40 (s, 9H, Boc).

 $^{13}$ C NMR of the mixture of Boc- and Cbz-rotamers (126 MHz, DMSO)  $\delta$  171.44 (s), 171.34 (s), 155.60 (s), 153.84 (s), 153.76 (s), 136.95 (s), 128.46 (s), 127.88 (s), 127.59 (s), 78.77 (s), 66.08 (s), 58.50 (s), 57.76 (s), 55.11 (s), 54.98 (s), 54.49 (s), 52.01 (s), 48.88 (s), 48.14 (s), 47.12 (s), 46.64 (s), 41.28 (s), 40.48 (s), 28.09 (s).

MS (CI, m/z): 405 (M+H+).

Anal. calcd for  $C_{21}H_{28}N_2O_6{:}$  C, 62.36; H, 6.98; N, 6.93. Found C, 61.98; H, 6.71; N, 6.59.

### 2,6-Diaza-spiro[3.4]octane-2,6,8-tricarboxylic acid 6-benzyl ester 2-tert-butyl ester (45)

A solution of **44** (2.00 g, 4.94 mmol) in a mixture of methanol (20 mL) and water (2 mL) was cooled to 0°C. Lithium hydroxide (0.23 g, 5.44 mmol, 1.1 eq.) was dissolved in water (2 mL) and added dropwise. The reaction mixture was stirred overnight (conversion was checked by NMR), evaporated, NaHSO<sub>4</sub> (0.71 g, 5.93 mmol, 1.2 eq.) was dissolved in water (10 mL) and added. The formed solution was extracted with ethyl acetate (3x10 mL), combined organic layers were washed with brine (30 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered over silica gel and evaporated to afford the title compound (1.74 g, 90% yield).

White solid. M. p. 148°C.

 $^{1}\text{H}$  NMR (400 MHz, DMSO)  $\delta$  12.82 (s, 1H, CO\_2H), 7.57 – 7.15 (m, 5H, Ph), 5.07 (s, 2H, OCH\_2Ph), 3.96 – 3.47 (m, 7H), 3.33 (s, 1H), 3.18 (s, 1H), 1.37 (s, 9H, Boc).



 $^{13}\text{C}$  NMR of the mixture of Boc- and Cbz-rotamers (126 MHz, DMSO)  $\delta$  172.55, 172.47 (2xs, CO<sub>2</sub>H), 155.62 (s), 153.87, 153.80 (2xs), 136.98 (s, Ph, C), 128.45 (s, Ph, CH), 127.85 (s, Ph, CH), 127.56 (s, Ph, CH), 78.71(s, C(CH\_3)\_3), 66.04 (s, OCH\_2Ph), 58.43, 57.65 (2xs, CCH\_2N), 55.39, 54.81 (2xs, CCH\_2N), 55.19, 54.71 (2xs), 49.01, 48.27 (2xs), 47.25, 46.78 (2xs), 41.07, 40.28 (2xs), 28.11 (C(CH\_3)\_3).

#### MS (CI, m/z): 389 (M-H+).

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Anal. calcd for  $C_{20}H_{26}N_2O_6{:}$  C, 61.53; H, 6.71; N, 7.18. Found: C, 61.69; H, 6.36; N, 6.91.

### (8S)-8-Acetoxymethyl-2-oxa-6-aza-spiro[3.4]octane-6-carboxylic acid tert-butyl ester ((S)-46)

Colorless oil. Purified by column chromatography (Hex/MTBE (67%/33%). 40% yield.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 4.78 (d, J = 6.0 Hz, 1H), 4.57 (m, 3H), 4.29 (s, 1H), 4.06 (m, 1H), 3.65 (m, 2H), 3.41 (m, 1H), 3.20 (m, 1H), 2.56 (s, 1H), 2.06 (s, 3H, COC*H*<sub>3</sub>), 1.44 (s, 9H, Boc).

 $^{13}\text{C}$  NMR of both Boc-rotamers (126 MHz, CDCl<sub>3</sub>)  $\delta$  170.90 (s, COCH<sub>3</sub>), 154.46 (s, CO<sub>2</sub><sup>t</sup>Bu), 81.59, 81.15 (2xs), 79.99 (s), 75.76 (s), 63.12 (s), 55.02 (s), 48.06 (s), 47.48 (s), 43.46, 42.58 (2xs), 28.56 (s, C(CH<sub>3</sub>)<sub>3</sub>), 20.94 (s, COCH<sub>3</sub>).

#### MS (EI, *m/z*): 285 (M<sup>+</sup>).

Anal. calcd for  $C_{14}H_{23}NO_5\!\!:C,\,58.93;\,H,\,8.13;\,N,\,4.91.$  Found: C, 58.65; H, 7.84; N, 5.17.

#### Benzyl (S)-8-((S)-4-benzyl-2-oxooxazolidine-3-carbonyl)-6azaspiro[3.4]octane-6-carboxylate (47)

A 12% solution of (4S)-benzyl-2-oxazolidinone (17.4 g, 98.5 mmol, 1.2 eq.) in THF was cooled to -50 °C under argon. n-butyllithium (43 mL, 1.3 eq., 2.5 M in hexanes) was slowly added by a dropping funnel. The reaction mixture was stirred at -50 °C for 1 h. The 10% solution of benzyl 8-(chlorocarbonyl)-6-azaspiro[3.4]octane-6-carboxylate (25.3 g, 82.1 mmol, 1.0 eq.) in THF was slowly cannulated to the oxazolidinone solution. The addition rate of the acid chloride solution was controlled so that the internal temperature was in the range between -40 to -50 °C. Reaction mixture was stirred at -40 to -50 °C for 6 h. Saturated NH<sub>4</sub>Cl solution (200 mL) was added to quench the reaction, and the reaction mixture was concentrated under reduced pressure. The residue was dissolved in a mixture of DCM (300 mL) and water (200 mL). Aqueous layer was separated and washed with DCM (5x200 mL). Combined organic layers were washed with cold 10% aqueous solution of K2CO3 (400 mL) and brine (400 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated to give the crude product. The crude product was purified by flash chromatography Hex/MTBE (40%/60%) to afford the title compounds (16.2 g, 44% yield of 47 and 16.9 g, 46% yield of 48).

Colorless oil. 96.7% de,  $[\alpha]^{20}$  =+14.5, retention time 36.71 min.

<sup>1</sup>H NMR of the mixture of both Cbz-rotamers (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.76 – 6.73 (m, 10H, 2xPh), 5.14 (m, 2H, CO<sub>2</sub>CH<sub>2</sub>Ph), 4.67 (m, 1H), 4.35 (d, *J* = 7.0 Hz, 1H), 4.19 (m, 2H), 3.84 – 3.40 (m, 4H), 3.32 (d, *J* = 13.0 Hz, 1H), 2.67 (t, *J* = 11.6 Hz, 1H), 2.37 – 1.76 (m, 6H).

 $^{13}\text{C}$  NMR of the mixture of both Cbz-rotamers (126 MHz, CDCl<sub>3</sub>)  $\delta$  172.42 (s), 172.40 (s), 154.94 (s), 154.73 (s), 153.57 (s), 153.53 (s), 136.88 (s), 136.86 (s), 135.17 (s), 135.15 (s), 129.35 (s), 129.02 (s), 128.47 (s), 127.93 (s), 127.86 (s), 127.43 (s), 66.86 (s), 66.83 (s), 66.24 (s), 66.22 (s), 56.62 (s), 56.45 (s), 55.45 (s), 49.83 (s), 49.16 (s), 48.19 (s), 47.92 (s), 47.59 (s), 47.27 (s), 38.32 (s), 38.26 (s), 34.64 (s), 34.32 (s), 26.71 (s), 16.49 (s), 16.40 (s).

MS (CI, m/z): 449 (M+H+).

Anal. calcd for  $C_{26}H_{28}N_2O_5{:}$  C, 69.63; H, 6.29; N, 6.25. Found: C, 69.90; H, 6.38; N, 6.57.

#### Benzyl (*R*)-8-((*S*)-4-benzyl-2-oxooxazolidine-3-carbonyl)-6azaspiro[3.4]octane-6-carboxylate (48)

Colorless oil. 97.7% de,  $[\alpha]^{20}$ <sub>D</sub> =+62.9, retention time 19.28 min.

<sup>1</sup>H NMR of the mixture of both Cbz-rotamers (400 MHz, CDCl<sub>3</sub>) δ 7.57 – 6.93 (m, 10H, 2xPh), 5.17 (m, 2H, CO<sub>2</sub>CH<sub>2</sub>Ph), 4.67 (m, 1H), 4.22 (m, 3H), 3.67 (m, 4H), 3.22 (t, J = 10.0 Hz, 1H), 2.83 – 2.69 (m, 1H), 1.98 (m, 6H).

 $^{13}$ C NMR of the mixture of both Cbz-rotamers (126 MHz, DMSO)  $\bar{\delta}$  172.46 (s), 172.25 (s), 154.96 (s), 154.80 (s), 153.53 (s), 153.49 (s), 136.97 (s), 136.88 (s), 135.04 (s), 135.00 (s), 129.47 (s), 129.07 (s), 129.02 (s), 128.53 (s), 128.02 (s), 127.97 (s), 127.89 (s), 127.49 (s), 66.92 (s), 66.90 (s), 66.37 (s), 66.35 (s), 56.93 (s), 56.71 (s), 55.27 (s), 55.25 (s), 50.52 (s), 49.73 (s), 48.56 (s), 48.02 (s), 47.63 (s), 46.87 (s), 37.81 (s), 34.84 (s), 34.55 (s), 27.01 (s), 26.99 (s), 16.49 (s), 16.40 (s).

MS (CI, *m/z*): 449 (M+H<sup>+</sup>).

Anal. calcd for  $C_{26}H_{28}N_2O_5{:}$  C, 69.63; H, 6.29; N, 6.25. Found: C, 69.77; H, 6.51; N, 6.02.

#### (S)-6-azaspiro[3.4]octane-8-carboxylic acid hydrochloride ((S)-49)

A 10% solution of **(S)-29** (1.03 g, 3.56 mmol) in ethanol, 5% palladium on charcoal (1.52 g, 0.71 mmol, 0.2 eq.) and NH<sub>4</sub>Cl (0.20 g, 3.74 mmol, 1.05 eq.) were mixed and stirred under H<sub>2</sub> (1 atm.) at room temperature overnight. Then, the reaction mixture was filtered through celite and the solvent was evaporated under reduced pressure to give the product (0.60 g, 99% yield).

### White crystals.

<sup>1</sup>H NMR (400 MHz, DMSO)  $\delta$  12.94 (broad s, 1H, COO*H*), 9.80 (broad s, 1H, N*H*), 9.55 (broad s, 1H, N*H*), 3.38 – 3.09 (m, 4H, N(C*H*<sub>2</sub>)<sub>2</sub>), 2.99 (t, *J* = 6.9 Hz, 1H, C*H*), 2.22 – 1.58 (m, 6H, C*H*<sub>2</sub>C*H*<sub>2</sub>C*H*<sub>2</sub>).

 $^{13}\text{C}$  NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  172.90 (s), 54.12 (s), 50.91 (s), 47.45 (s), 45.44 (s), 30.89 (s), 27.08 (s), 15.69 (s).

MS (CI, m/z): 156 (M-CI<sup>-</sup>).

Anal. calcd for  $C_8H_{14}CINO_2:$  C, 50.14; H, 7.36; N, 7.31. Found: 49.87; H, 7.55; N, 7.63.

# tert-Butyl (S)-(6-azaspiro[3.4]octan-8-yl)carbamate hydrochloride ((S)-50)

A mixture of **(S)-29** (10.9 g, 37.6 mmol), DPPA (8.9 mL, 41.4 mmol, 1.1 eq.) and triethylamine (6.3 mL, 45.1 mol, 1.2 eq.) in tert-butanol (120 mL) was stirred overnight at 80 °C. Reaction mixture was evaporated and mixture of brine: ethyl acetate (100:200 mL) was added. Brine layer was extracted ethyl acetate (3x100 mL). Combined organic layers were washed with cold 10% aqueous solution of KOH (200 mL) twice, dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated under reduced pressure. The residue was recrystallized from methyl tert-butyl ether. To obtained precipitate in methanol (150 mL) activated charcoal (2.2 g) was added and suspension was refluxed for 10 min and filtered through SiO<sub>2</sub>. Then, 5% palladium on charcoal (16.0 g, 7.52 mmol, 0.2 eq.) and NH<sub>4</sub>Cl (2.1 g, 39.5 mmol, 1.05 eq.) were mixed and stirred under H<sub>2</sub> (1 atm.) at room temperature overnight. Afterwards, the reaction mixture was filtered through celite and the solvent was evaporated to give the title compound (4.26 g, 50% yield).

White solid. M. p. 117-120°C.  $[\alpha]^{20}_{D}$  =-37.6.

<sup>1</sup>H NMR (400 MHz, DMSO) δ 9.28 (broad s, 2H), 7.18 (2xs, 1H), 4.01 (m, 1H), 3.43 - 3.22 (m, 3H), 2.93 (dd, J = 12.0, 4.5 Hz, 1H), 2.06 - 1.70 (m, 6H), 1.39 (s, 9H).

 $^{13}\text{C}$  NMR (101 MHz, DMSO)  $\delta$  155.92 (s), 78.71 (s), 56.35 (s), 52.77 (s), 47.83 (s), 47.44 (s), 30.49 (s), 28.59 (s), 24.88 (s), 15.52 (s).

MS (CI, m/z): 227 (M-CI-).

Anal. calcd for  $C_{12}H_{23}CIN_2O_2:$  C, 54.85; H, 8.82; N, 10.66. Found: C, 54.61; H, 8.49; N, 10.21.

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### Saturated heterocycles

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Synthesis of 6-azaspiro[4.3]alkanes: innovative scaffolds for drug discovery.

Novel scaffolds for drug discovery -6-azaspiro[4.3]alkanes - have been synthesized in two steps from four-membered ketones: cyclobutanone, thienone, N-Boc-azetidinone, *etc.* The key transformation was the reaction between electron-deficient exocyclic alkenes with *in situ* generated *N*-benzyl azomethine ylide.