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Ring-Rearrangement Metathesis of 1-Substituted 7-Azanorbornenes as an Entry to 1-Azaspiro[4.5]decane systems

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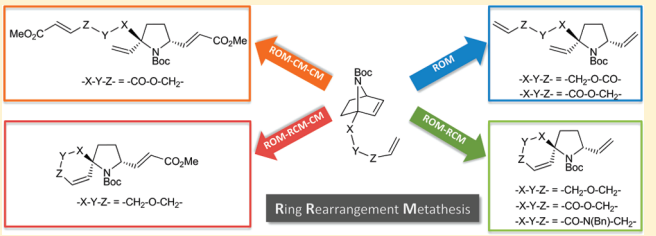
Supporting Information

ABSTRACT: Several metathesis sequences have been carried out using 7-azanorbornenes as starting materials. The occurrence of several exocyclic olefin patterns in the bridgehead position of this system opens the way to gain interesting spirocyclic compounds, which were achieved using several ring-rearrangement metatheses (RRM). The metathesis products, thus obtained, may be useful for the synthesis of new peptidomimetics and related compounds.



INTRODUCTION

The progress of tandem metathesis reactions has allowed the straightforward construction of complex organic molecules with a significant atom economy.[1] In this sense, the development of well-defined catalysts, tolerant to most functional groups, has made it possible to extend these processes to new substrates. Combinations of several metathesis steps are also possible. Among the domino reactions, ring-rearrangement metathesis (RRM),[2] involving ring-opening/ring-closing metathesis (ROM/RCM) steps, has been effectively applied to the construction of carbo- and heterocycles and has been used as a key step in several total syntheses of natural products,[3] where it has shown a high efficiency.

The RRM processes of norbornene[4] or oxanorbornene[5] derivatives have received a great deal of attention because they represent a powerful entry for the synthesis of highly substituted bicyclic compounds with complete stereochemistry control. However, there are only a few examples using azanorbornenes[6] as starting materials in RRM reactions and only two cases with 7-azanorbornenes.[7]

Also, in the most of the above-mentioned examples, linear fused bicyclic systems were obtained, setting the exocyclic double bond in position 2 or 3 of the starting material, but if the exocyclic double bond is located at the bridgehead position, we could obtain spiro-fused systems. We have only found two recent reports concerning this methodology with norbornene,[8] oxanorbornene,[8] and oxabicyclo[3.2.1]octene derivatives.[9]

Spirocyclic compounds are remarkable synthetic targets in organic chemistry and are used as scaffolds in medicinal chemistry due to their conformational rigidity.[10] Many natural compounds possess a spiro linkage as a structural element, including the subclass of spirocyclic ethers and spirocyclic amides. In particular, the 1-azaspiro[4.5]decane systems and related structures have been observed in a great number of alkaloid natural products.[10d] Several methods have been described for the construction of 1-azaspirocyclic ring systems, but few of them have considered to include an additional heteroatom in the six-membered ring.

Furthermore, the 7-aza-1-oxaspiro[4.5]decane core **A** has emerged as a key substructure in the synthesis of a neurokinin-1 (NK-1) receptor antagonist (Figure 1). An efficient enantioselective synthesis of this compound via a double ring-closing metathesis strategy has been developed by Wallace et al.[11] In this field, several compounds that contain the 1,7-diazaspiro[4.5]decane core **B** have been used in the study of NK-1 activity[12] (Figure 1). Another relevant spirocyclic substructure, the 7-oxa-1-azaspiro-[4.5]decane core **C**, is present in the compound (+)-*S* 21552, a new therapeutic agent that showed a very good affinity and high selectivity for the 5-HT_{1A} receptor,[13] a subtype of the serotonin or 5-hydroxytryptamine (5-HT) neurotransmitter of the nervous central system (Figure 1).

In this paper, taking into account these facts, our goal involves the development of new strategies to gain different derivatives that contain 1,7-diazaspiro[4.5]decane and 7-oxa-1-azaspiro[4.5]decane skeletons, by the use of RRM processes. Therefore, the retrosynthetic pathway of the synthesis of some of these important spirocyclic systems is illustrated in Scheme 1. The first reaction, which is the key step in our synthetic pathway, involves ROM/RCM processes of 1-substituted 7-azanorbornene systems. This strategy opens up an alternative route to access these compounds.

Recently, as a part of our research project on the metathesis chemistry of azanorbornenes, we have studied the ring-opening metathesis-cross metathesis reaction (ROCM) of methyl *N*-Boc-7-azabicyclo[2.2.1]hept-2-en-1-carboxylate[14] and the influence of the electronic features of the olefin cross-partner.[15] Because of the importance of a general entry to the synthesis of 1-azaspiro[4.5]decane derivatives, we now considered application of the RRM sequence to bridgehead-substituted 7-azanorbornene systems, using the most common ruthenium catalysts shown in Figure 2.

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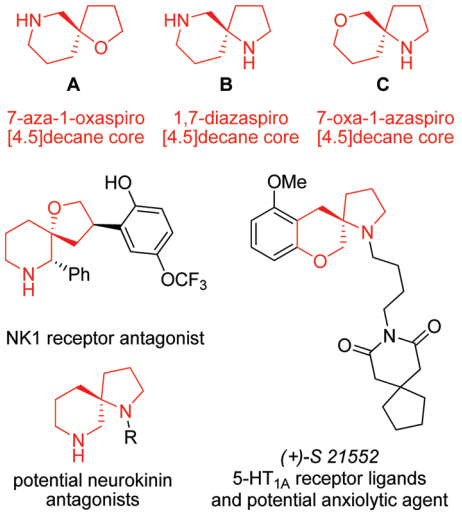
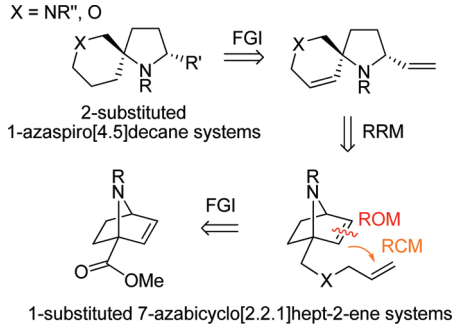


Figure 1. Bioactive molecules containing spiro[4.5]decane cores.

Scheme 1. Retrosynthetic Pathway of 2-Substituted 1-Azaspiro[4.5]decane Systems



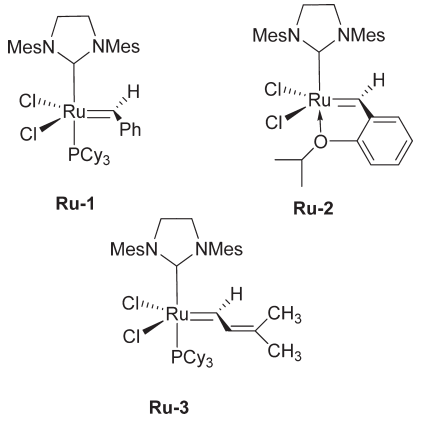
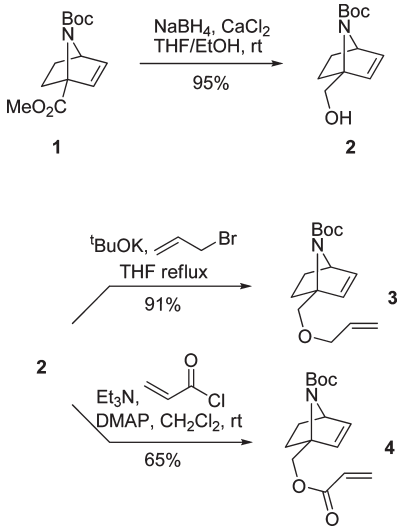


Figure 2. Catalysts used in this work.

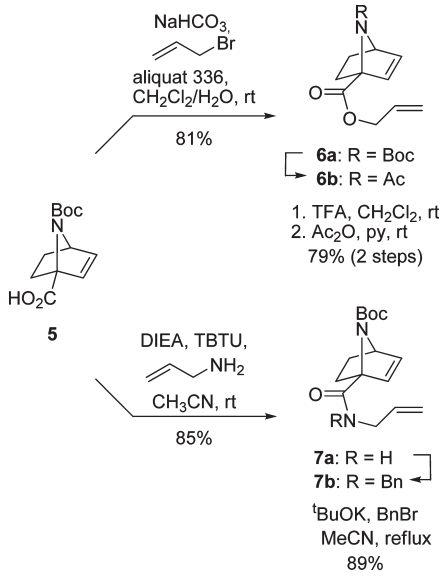
RESULTS AND DISCUSSION

For this purpose, several metathesis precursors were synthesized from the starting material methyl *N*-Boc-7-azabicyclo-[2.2.1]hept-2-en-1-carboxylate **1**, which is available in both racemic[14a] and enantiomeric[14b] versions. Reduction of ester **1** with $Ca(BH_4)_2$ generated *in situ* gives the primary alcohol **2** in a good yield. This compound was converted to allyl ether **3** (91%) using allyl bromide in THF. On the other hand, compound **2** was transformed in acrylate **4** (65%) by esterification with acryloyl chloride, DMAP, and Et_3N in CH_2Cl_2 (Scheme 2).

Scheme 2. Synthesis of Metathesis Precursors 3 and 4



Scheme 3. Synthesis of Metathesis Precursors 6 and 7



Alternatively, saponification of ester **1** with LiOH led to acid **5**,[14b] which opens the way to new derivatives. This acid was treated with allyl bromide, using Aliquat 336 as a phase-transfer catalyst in a CH_2Cl_2/H_2O mixture, to afford allyl ester **6a** in 81% yield. In order to evaluate the behavior of the protecting group in the metathesis processes, the amine protecting group was changed to acetamide by removing the Boc group with TFA and treating the salt with Ac_2O and pyridine to obtain **6b** in good yield (Scheme 3).

On the other hand, acid **5** was also the starting material that led us to allyl amide **7a** (85%) reacting with allyl amine using TBTU and DIEA. The structure of this compound was unambiguously confirmed by X-ray diffraction (see Supporting Information).

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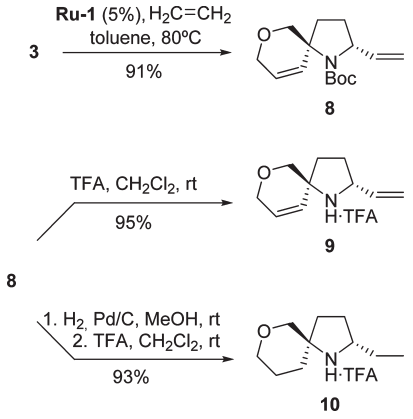
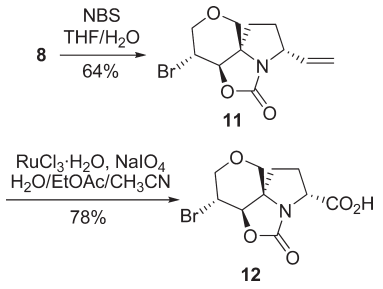
Scheme 4. ROM-RCM Process on Compound 3



Scheme 5. Derivatization of Compound 8

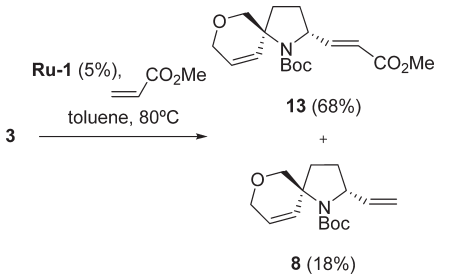


Subsequent benzylation of the allyl amide with BnBr and ^{t}BuOK in THF provided compound **7b** in 89% yield (Scheme 3). Thus, we have gained access to six different substrates (compounds **3**, **4**, **6a**, **6b**, **7a**, and **7b**) with double bonds conveniently arranged to try the RRM processes.

With compound **3** in our hands, we examined its ROM-RCM reactivity, and therefore this compound was treated with the second-generation Grubbs catalyst (**Ru-1**), in toluene at 80 °C under an atmosphere of ethylene. Subsequently, the desired spiro compound **8** was obtained with an excellent yield as a result of a ROM-RCM process. The structure was confirmed by NMR experiments at 340 K (because the NMR signals appeared duplicated at room temperature; see Supporting Information) and by removing the Boc group with TFA to obtain amine **9**. The saturated amine **10** was also synthesized after hydrogenation of the spiro compound **8**, using Pd/C as a catalyst in MeOH, and subsequent Boc group removal using TFA conditions (Scheme 4). As discussed in the Introduction, the synthesized substructure, 7-oxa-1-azaspiro[4.5]decane, is featured in bioactive compounds such as a serotonin agonist[13] and emerges in patented products with herbicide or pesticide properties.[16]

In order to gain some differentiation between both double bonds in compound **8**, we carried out a strategy previously used by Rainer et al.[7a] because the use of conventional regioselective oxidative fragmentation methodology resulted in a complete decomposition of the substrate. Therefore, we treated the spirocyclic compound **8** with NBS in THF/H_2O to give the cyclic carbamate **11** (Scheme 5). Surprisingly, and contrary to the reaction described by Rainer et al., the carbamate is formed in the endocyclic olefin probably because of the stereoelectronic and conformational characteristics of compound

Scheme 6. ROM-RCM-CM Process on Compound 3



8 structure and particularly the increase of electronic density in the disubstituted double bond with regard to the monosubstituted one. Therefore, bromine will prefer to attack preferentially this double bond by the more accessible face. The stereochemistry was established by NMR experiments and corroborated by transformation of carbamate **11** to acid **12** by means of the oxidation of exocyclic double bond with RuO_4, generated *in situ*. The structure and the stereochemistry were unambiguously confirmed by X-ray diffraction from the corresponding monocrystal of compound **12** (see Supporting Information).

The domino processes (ROM-RCM) discussed above only concern intramolecular reactions. The expansion of the intramolecular domino metathesis processes to an intermolecular reaction, cross metathesis (CM), was also applied on compound **3** to provide a typical ROM-RCM-CM sequence. The reaction was achieved in similar conditions, with catalyst **Ru-1** in toluene at 80 °C, but now using methyl acrylate as a cross metathesis partner. We obtained a mixture of ROM-RCM-CM adduct **13** in a 68% yield and the previously reported ROM-RCM compund **8** in a 18% yield after column chromatography. Other reaction conditions were attempted to increase the yield of compound **13** with negative results (Scheme 6).

The structure of **13**, with an excellent stereoselectivity (only *E* isomer), was confirmed by NMR experiments at 340 K and by removing the Boc group to obtain amine **14**. Compound **13** is an important intermediate to obtain new γ-amino acids. Consequently, concomitant hydrolysis of Boc and methyl ester groups in an acid medium allowed us to obtain amino acid hydrochloride **15** after 5 days in 94% yield. The reaction time could be shortened by a basic hydrolysis of the methyl ester group and by removing the Boc group with HCl to give **15** in 86% yield (two steps). On the other hand, hydrogenation of compound **13** with Pd−C as a catalyst and subsequent hydrolysis of the Boc group with TFA gave the salt **16**. The later acid hydrolysis of the methyl ester group afforded the saturated amino acid **17** as a hydrochloride (Scheme 7). It is important to note that these two novel amino acids (**15** and **17**) carry the substructure of GABA[17] (an inhibitory neurotransmitter found in the nervous system) with a limited flexibility due to the restriction imposed by the spirocycle system. Related compounds have been synthesized and their affinities to the GABA transport proteins GAT-1 and GAT-3 have been evaluated.[18]

In the next step of this work, the RRM of 7-azanorbornene **6a** was then investigated. In the same conditions used with allyl ether **3** and using **Ru-1** as a catalyst, we obtained compound **18a** (77% yield) as the consequence of the ROM process (Scheme 8). Changes in the catalyst gave the same product but with an improved yield: 81% yield employing catalyst **Ru-2** and 88% yield with catalyst **Ru-3**. In order to evaluate the effect of the

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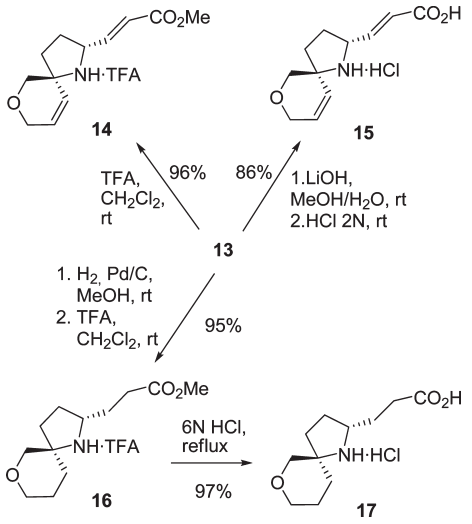
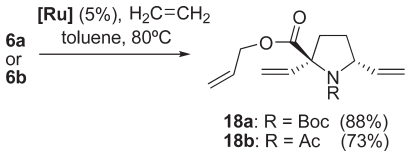
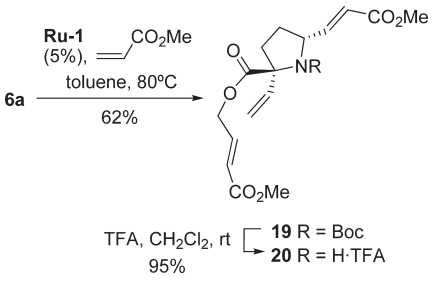
Scheme 7. Transformations of Spirocyclic 13



Scheme 8. ROM Process on Compounds 6a,b



Scheme 9. ROM-CM-CM Process on Compound 6a

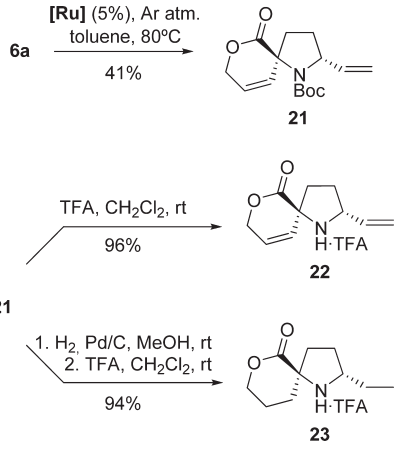


Boc group, we carried out the reaction with azanorbornene **6b**, giving compound **18b** with the same ROM reactivity but lesser yield (73%). To gain the spirocyclic compound, we also examined the possibility to carry out a RCM reaction with **18a** or **18b**, but all of the different conditions used gave the starting materials.

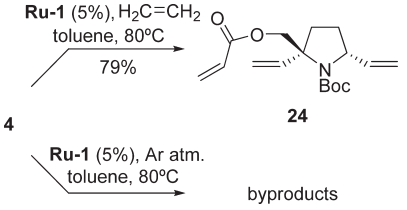
When the same substrate **6a** was subjected to the ROM-RCM-CM conditions, using the methyl acrylate as a cross metathesis partner, pyrrolidine **19** was obtained (Scheme 9). We could not find any traces of the spirocyclic compound and diester **19** was the result of a ROM-CM-CM process with both double bonds with *E* configuration. The structure of **19** was confirmed by NMR experiments at 340 K and by removing the Boc group to obtain salt **20**. The structure of **20** was confirmed by X-ray diffraction (see Supporting Information).

Fortunately, without the atmosphere of ethylene and using argon atmosphere, spiro compound **21** could be obtained, although with a moderate yield (39%) with catalyst **Ru-1** (Scheme 10). The yield could not be significantly improved by the use of catalyst **Ru-3** (41%).

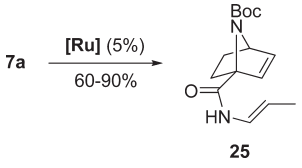
Scheme 10. ROM-RCM Process on Compound 6a



Scheme 11. ROM Processes on Compound 4



Scheme 12. Isomerization Process of Compound 7a



The structure was confirmed by NMR experiments at 340 K and by removing the Boc group with TFA to obtain salt **22**. This substructure, lacking the vinyl group, has been synthesized by Rubiralta et al. as a part of their peptidomimetic research.[19] Saturated compound **23** was also synthesized in an excellent yield after hydrogenation of **21**, using Pd/C as a catalyst in MeOH, and by removing the Boc group with TFA.

Following the study of the RRM processes, when azanorbornene **4** was exposed to the second generation Grubbs catalyst (**Ru-1**) in toluene at 80 °C under an atmosphere of ethylene, the spiro compound was not observed, pyrrolidine **24** being obtained by a ROM process (Scheme 11). The use of other catalyst gave the same ROM product. For this precursor **4**, we also tried the reaction in the absence of ethylene and in argon atmosphere, but in this case no expected product was observed.

In the last case, the RRM of 7-azanorbornene **7a** was then investigated. The conditions that had been successful with **3** were tried, producing the isomerization of the double bond in a nonreproducible reaction to give compound **25** (Scheme 12). This reactivity had been formerly studied by Alcaide et al. for allyl amides and allyl amines.[20]

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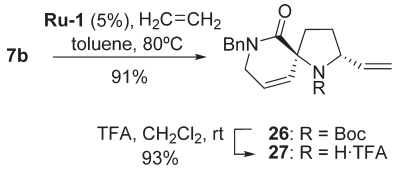
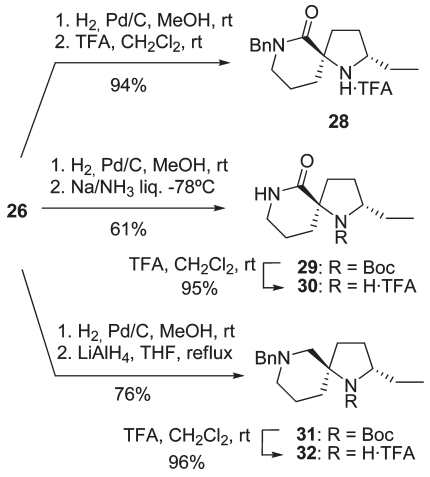
Scheme 13. ROM-RCM Process on Compound 7b



Scheme 14. Transformations of Compound 26



In order to avoid the isomerization reaction, we tried the metathesis process using the protected precursor **7b**, which was treated in the same conditions, leading to the spiro compound **26** in an excellent yield (91%). The structure was confirmed by NMR experiments at 340 K and by removing the Boc group to obtain the salt **27** (Scheme 13). Structure **26** could be regarded as a peptidomimetic precursor. In fact, this structure without the vinyl substituent has shown a peptidomimetic-like utility.[19] In this sense, the synthesis of Freidinger lactam,[21] the first case to obtain a β-sheet in peptides, opened the way to the synthesis of novel peptidomimetics that contain the proline core,[22] including spirocyclic structures such as **26** and **27**.

We have shown that these RRM reactions are a suitable route to obtain 1,7-diazaspiro compounds. The next step was to evaluate the orthogonal protection of functional groups. Consequently, hydrogenation of compound **26**, using Pd/C as a catalyst in MeOH, and subsequent hydrolysis of the Boc group gave the corresponding saturated compound **28** (Scheme 14). Starting again from compound **26** and after hydrogenation, the benzyl group could be removed using sodium in liquid ammonium at −78 °C to obtain amide **29** in a moderate yield. Additionally, Boc group of **29** was removed leading to diaza-compound **30**.

Starting from compound **26**, we carried out the synthesis of a new spirocyclic diamine structure. These compounds have attracted attention because of their biological and pharmacologic activities.[23] After hydrogenation of compound **26**, the amide of the saturated compound could be reduced with an excess of $LiAlH_4$, giving compound **31** in 76% yield (Scheme 14). The structure was confirmed by NMR experiments and by removing the Boc group to obtain salt **32**.

CONCLUSION

A variety of RRM metathesis processes have been studied using several 1-substituted 7-azanorbornenes as starting materials. All of these strategies have proven to be a very efficient and versatile method for the construction of heterocyclic structures such as interesting 1-azaspirocyclic compounds with a large atom economy. Some of these products thus obtained may be useful for the synthesis of new peptidomimetics and related compounds; in particular, these reactions could be extended to their enantiomeric versions, because of the availability of the starting material, compound **1**, in its enantiopure form.[14b]

EXPERIMENTAL SECTION

General Procedures. Solvents were purified according to standard procedures. Column chromatography was performed using silica gel 60 (230−400 mesh). ^{1}H and ^{13}C NMR spectra were recorded on 300 and 400 MHz spectrometers. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ with TMS as internal reference, DMSO-d_6 and D_2O (chemical shifts are reported in ppm on the δ scale, and coupling constants are in Hz). Assignment of all separate signals in the ^{1}H NMR spectra was made on the basis of coupling constants and ge-COSY and ge-HSQC experiments on a 400 MHz spectrometer. Melting points were determined on a melting point apparatus and are uncorrected. Electrospray mass spectra were recorded on a microQTof spectrometer; accurate mass measurements were achieved using sodium formate as an external reference.

(1*R*,4*S*)- and (1*S*,4*R*)-7-Boc-1-hydroxymethyl-7-azabicyclo[2.2.1]hept-2-ene (2). To a solution of methyl ester **1** (188 mg, 0.74 mmol) and $CaCl_2$ (165 mg, 1.48 mmol) in EtOH/THF (6:4, 10 mL) at 0 °C, $NaBH_4$ (112 mg, 2.96 mmol) was added. The suspension was stirred at rt for 7 h. The mixture was diluted with EtOAc (10 mL) and washed with 5% aqueous K_2CO_3 (15 mL), 0.5 N HCl (15 mL), and saturated NaCl (15 mL). The organic layer was dried, filtered, and evaporated. The residue was purified by column chromatography, using hexane/EtOAc (8:2) as eluent, to give alcohol **2** (159 mg, 95%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.07−1.21 (m, 2H, CH_2), 1.43 (s, 9H, $C(CH_3)_3$), 1.87−1.96 (m, 2H, CH_2), 4.08−4.23 (m, 2H, CH_2-OH), 4.68−4.76 (m, 1H, CH), 6.20 (d, 1H, J = 5.8 Hz, CH_{vin}), 6.28 (dd, 1H, J = 2.1, 5.8 Hz, CH_{vin}). ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.0 (CH_2), 26.6 (CH_2), 28.3 ($C(\underline{C}H_3)_3$), 61.3 (CH), 61.4 (CH_2-OH), 73.4 (C), 80.6 ($\underline{C}(CH_3)_3$), 134.9 (CH_{vin}), 136.7 (CH_{vin}), 154.8 (CO_{Boc}). HRMS (ESI) calcd for $C_{12}H_{19}NO_3Na$ $[M + Na]^+$: 248.1263, found 248.1251.

(1*R*,4*S*)- and (1*S*,4*R*)-7-Boc-1-allyloxymethyl-7-azabicyclo[2.2.1]hept-2-ene (3). To the stirred suspension of alcohol **2** (280 mg, 1.24 mmol) in anhydrous THF (20 mL), allyl bromide (0.16 mL, 1.86 mmol) and potassium *tert*-butoxide (1.5 mL, 1 M in THF) were added. The reaction was stirred for 14 h at 60 °C. The mixture was cooled, treated carefully with water (10 mL) until complete solution, and extracted with Et_2O (3 × 15 mL). The combined organic layers were dried, filtered, and evaporated. The remaining residue was purified by column chromatography, using hexane/EtOAc (9:1) as eluent, to give ether **3** (300 mg, 91%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13−1.24 (m, 1H, CH_2), 1.31−1.38 (m, 1H, CH_2), 1.41 (s, 9H, $C(CH_3)_3$), 1.71−1.81 (m, 1H, CH_2), 1.85−1.97 (m, 1H, CH_2), 4.06−4.15 (m, 3H, O-CH_2), 4.22−4.31 (m, 1H, O-CH_2), 4.64−4.71 (m, 1H, CH), 5.15−5.22 (m, 1H, CH_{2allyl}), 5.26−5.35 (m, 1H, CH_{2allyl}), 5.88−6.03 (m, 1H, CH_{allyl}), 6.23 (dd, 1H, J = 5.9, 2.2 Hz, CH_{vin}), 6.29 (d, 1H, J = 5.8 Hz, CH_{vin}). ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.0 (CH_2), 28.2 ($C(\underline{C}H_3)_3$), 28.8 (CH_2), 61.4 (CH), 67.1 (C), 70.0 (O-CH_2), 72.5 (O-CH_2), 79.8 (C_{Boc}), 116.8 (CH_{2allyl}), 133.7 (CH_{vin}), 135.0 (CH_{allyl}), 136.8 (CH_{vin}), 154.7 (CO_{Boc}). HRMS (ESI) calcd for $C_{15}H_{23}NO_3Na$ $[M + Na]^+$: 288.1576, found 288.1570.

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(1*R*,4*S*)- and (1*S*,4*R*)-7-Boc-1-(acryloyloxymethyl)-7-azabicyclo[2.2.1]hept-2-ene (4). To the stirred suspension of alcohol **3** (170 mg, 0.75 mmol) in CH_2Cl_2 (14 mL), Et_3N (0.18 mL, 1.51 mmol), DMAP (18 mg, 0.15 mmol), and acryloyl chloride (73 μL, 0.91 mmol) were added. The reaction was stirred at rt for 13 h. The mixture was treated with 2 N HCl (8 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried, filtered, and evaporated. The remaining residue was purified by column chromatography, using hexane/EtOAc (8:2) as eluent, to give ester **4** as a yellow oil (138 mg, 65%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15−1.25 (m, 1H, CH_2), 1.26−1.35 (m, 1H, CH_2), 1.41 (s, 9H, $C(CH_3)_3$), 1.77−1.87 (m, 1H, CH_2), 1.90−2.00 (m, 1H, CH_2), 4.70−4.78 (m, 1H, CH), 4.84−5.02 (m, 2H, CH_2), 5.85 (dd, 1H, *J* = 10.4, 1.6 Hz, CH_{2vin}), 6.13−6.25 (m, 2H, CH_{vinAza} + CH_{vin}), 6.30 (dd, 1H, *J* = 5.8, 2.3 Hz, CH_{vinAza}), 6.45 (dd, 1H, *J* = 17.3, 1.5 Hz, CH_{2vin}). ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.7 (CH_2), 28.2 ($C(\underline{C}H_3)_3$), 33.4 (CH_2), 61.4 (CH), 63.9 (CH_2), 69.9 (C), 80.3 (C_{Boc}), 128.2 (CH_{vin}), 131.1 (CH_{2vin}), 134.7 (CH_{vinAza}), 135.9 (CH_{vinAza}), 154.5 (CO_{Boc}), 166.0 (CO_{ester}). HRMS (ESI) calcd for $C_{15}H_{21}NO_4Na$ $[M + Na]^+$: 302.1368, found 302.1363.

(1*R*,4*S*)- and (1*S*,4*R*)-7-Boc-7-azabicyclo[2.2.1]hept-2-ene-1-carboxylic Acid Allyl Ester (6a). Acid **5** (140 mg, 0.58 mmol) and $NaHCO_3$ (49 mg, 0.58 mmol) were dissolved in water (5 mL), and a solution of tricaprylmethylammonium chloride (Aliquat 336) (0.27 mL, 0.58 mmol) and allyl bromide (0.27 mL, 0.58 mmol) in CH_2Cl_2 (5 mL) was added. After being stirred vigorously at rt for 3 days, the reaction mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried, filtered, and evaporated. The remaining residue was purified by column chromatography, using hexane/EtOAc (7:3) as eluent, to give ester **6a** as a colorless oil (132 mg, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15−1.24 (m, 1H, CH_2), 1.37 (s, 9H, $C(CH_3)_3$), 1.43−1.51 (m, 1H, CH_2), 2.02−2.12 (m, 1H, CH_2), 2.21−2.30 (m, 1H, CH_2), 4.71−4.80 (m, 3H, CH + O-CH_2), 5.25 (d, 1H, *J* = 10.4 Hz, CH_{2allyl}), 5.37 (d, 1H, *J* = 17.2 Hz, CH_{2allyl}), 5.92−6.04 (m, 1H, CH_{allyl}), 6.31 (d, 1H, *J* = 5.4 Hz, CH_{vin}), 6.45 (d, 1H, *J* = 5.6 Hz, CH_{vin}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.7 (CH_2), 28.0 ($C(\underline{C}H_3)_3$), 29.3 (CH_2), 62.7 (CH), 65.7 (O- CH_2), 72.6 (C), 81.1 (C_{Boc}), 118.3 (CH_{2allyl}), 131.9 (CH_{allyl}), 134.6 (CH_{vin}), 135.0 (CH_{vin}), 155.9 (CO_{Boc}), 169.6 (CO_2). HRMS (ESI) calcd for $C_{15}H_{21}NO_4Na$ $[M + Na]^+$: 302.1363, found 302.1370.

(1*R*,4*S*)- and (1*S*,4*R*)-7-Acetyl-7-azabicyclo[2.2.1]hept-2-ene-1-carboxylic Acid Allyl Ester (6b). To a solution of **6a** (42 mg) in CH_2Cl_2 (10 mL), trifluoroacetic acid (0.5 mL) was added. The reaction mixture was stirred at rt for 3 h, and the solvent was removed under reduced pressure. The residue was dissolved in pyridine (4 mL), and anhydride acetic was added (2 mL). After stirring at rt for 7 h, the solvent was removed under reduced pressure. The residue was dissolved in toluene (2 × 5 mL) and then evaporated. The compound was purified by silica gel column chromatography eluting with hexane/EtOAc (4:6) to give the corresponding amide **6b** (25 mg, 79%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28−1.37 (m, 1H, CH_2), 1.42−1.51 (m, 1H, CH_2), 1.95 (s, 3H, $COCH_3$), 2.00−2.09 (m, 1H, CH_2), 2.25−2.35 (m, 1H, CH_2), 4.67−4.80 (m, 3H, CH + O-CH_2), 5.24 (d, 1H, *J* = 12.0 Hz, CH_{2allyl}), 5.36 (d, 1H, *J* = 14.7 Hz, CH_{2allyl}), 5.93−6.06 (m, 1H, CH_{allyl}), 6.32 (dd, 1H, *J* = 5.6, 1.5 Hz, CH_{vin}), 6.49 (d, 1H, *J* = 1.5 Hz, CH_{vin}). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5 ($CO\underline{C}H_3$), 26.4 (CH_2), 27.3 (CH_2), 61.9 (CH), 66.1 (O-CH_2), 70.9 (C), 118.5 (CH_{2allyl}), 132.0 (CH_{allyl}), 134.0 (CH_{vin}), 136.1 (CH_{vin}), 169.1, 171.0 (CO_{ester}, CO_{amida}). HRMS (ESI) calcd for $C_{12}H_{15}NO_3Na$ $[M + Na]^+$: 244.0944, found 244.0948.

(1*R*,4*S*)- and (1*S*,4*R*)-7-Boc-7-azabicyclo[2.2.1]hept-2-ene-1-carboxylic Acid Allyl Amide (7a). A solution of the acid **5** (200 mg, 0.84 mmol) in acetonitrile (15 mL) was treated with diisopropilethylamine (DIEA) (0.7 mL, 4.2 mmol), allylamine (82 μL, 1.09 mmol), and *O*-benzotriazol-1-yl-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) (350 mg, 1.09 mmol). The reaction mixture was stirred at rt for 14 h, the solvent was then removed, and the mixture was partitioned between 2 N HCl (20 mL) and ethyl acetate (20 mL). The aqueous layer was extracted with ethyl acetate (3 × 20 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to give a residue, which was purified by silica gel column chromatography, eluting with hexane/EtOAc (2:8) to give **7a** (210 mg, 85%) as a white solid. Mp: 65−66 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18−1.28 (m, 1H, CH_2), 1.39 (s, 9H, $C(CH_3)_3$), 1.49−1.58 (m, 1H, CH_2), 1.93−2.04 (m, 1H, CH_2), 2.07−2.18 (m, 1H, CH_2), 3.92−4.00 (m, 2H, CH_2-allyl), 4.68−4.74 (m, 1H, CH), 5.10−5.17 (m, 1H, CH_{2allyl}), 5.18−5.28 (m, 1H, CH_{2allyl}), 5.80−5.95 (m, 1H, CH_{allyl}), 6.13−6.23 (m, 1H, NH), 6.28 (dd, 1H, *J* = 5.8, 2.3 Hz, CH_{vin}), 6.33 (d, 1H, *J* = 5.8 Hz, CH_{vin}). ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.0 (CH_2), 27.4 (CH_2), 28.0 ($C(\underline{C}H_3)_3$), 41.8 (CH_{2allyl}), 62.7 (CH), 73.9 (C), 81.2 ($\underline{C}(CH_3)_3$), 116.3 (CH_{2allyl}), 134.1 (CH_{allyl}), 134.2 (CH_{vin}), 136.1 (CH_{vin}), 155.9 (CO_{Boc}), 169.7 (CO_{amide}). HRMS (ESI) calcd for $C_{15}H_{22}N_2O_3Na$ $[M + Na]^+$: 301.1523, found 301.1524.

(1*R*,4*S*)- and (1*S*,4*R*)-7-Boc-7-azabicyclo[2.2.1]hept-2-ene-1-carboxylic Acid Allyl Benzyl Amide (7b). To the stirred solution of allyl amide **7a** (200 mg, 0.72 mmol) in acetonitrile (20 mL), potassium *tert*-butoxide (2.8 mL, 1 M in THF) and benzyl bromide (0.13 mL, 1.08 mmol) were added. The reaction was stirred for 16 h at 70 °C. The mixture was evaporated, and the remaining residue was purified by column chromatography, using hexane/EtOAc (6:4) as eluent, to give benzyl amide **7b** (235 mg, 89%) as a colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.09−1.28 (m, 2H, CH_2), 1.37 (s, 9H, $C(CH_3)_3$), 1.73−1.88 (m, 1H, CH_2), 2.16−2.26 (m, 1H, CH_2), 3.87−4.07 (m, 1H, N-CH_2-allyl), 4.16−4.28 (m, 1H, N-CH_2-allyl), 4.60−4.82 (m, 3H, CH + CH_2-Bn), 4.98−5.17 (m, 2H, CH_{2allyl}), 5.63−5.80 (m, 1H, CH_{allyl}), 6.24−6.45 (m, 2H, CH_{vin}), 7.18−7.37 (m, 5H, Ph). ^{13}C NMR (100 MHz, DMSO-d_6) δ 24.5 (CH_2), 27.4 (CH_2), 28.2 ($C(\underline{C}H_3)_3$), 47.6 (N-CH_2-Allyl), 49.3 (CH_2−Ph), 62.3 (CH), 73.0 (C), 80.6 ($\underline{C}(CH_3)_3$), 118.6 (CH_{2allyl}), 127.2, 127.6, 128.0, 128.2, 128.7 (5 × C_{Ph}), 133.2, 133.8 (2 × CH_{vin}), 134.5 (CH_{allyl}), 154.9 (CO_{Boc}), 168.3 (CO_{amide}). HRMS (ESI) calcd for $C_{22}H_{28}N_2O_3Na$ $[M + Na]^+$: 391.1992, found 391.1985.

(2*R*,5*S*)- and (2*S*,5*R*)-1-Boc-7-oxa-2-vinyl-1-azaspiro[4.5]-dec-9-ene (8). A solution of **3** (110 mg, 0.41 mmol) and Grubbs second generation catalyst (18 mg, 0.02 mmol) in toluene (12 mL) was saturated with ethylene and left under an ethylene atmosphere (1 atm). The mixture was stirred at 80 °C for 8 h. The solvent was removed under reduced pressure, and the residue was purified by column chromatography using hexane/EtOAc (8:2) as eluent, to give spiro compound **8** (100 mg, 91%) as a colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.37 (s, 9H, $C(CH_3)_3$), 1.52−1.61 (m, 1H, CH_2), 1.66−1.78 (m, 1H, CH_2), 1.55−2.07 (m, 2H, CH_2), 3.49 (d, 1H, *J* = 10.3 Hz, C-CH_2-O), 3.85 (d, 1H, *J* = 9.6 Hz, C-CH_2-O), 3.99 (s, 2H, CH_2), 4.27−4.34 (m, 1H, CH), 5.01−5.10 (m, 2H, CH_{2vin}), 5.66−5.73 (m, 2H, 2 × CH_{vin}), 5.77−5.87 (m, 1H, CH_{vin}). ^{13}C NMR (100 MHz, DMSO-d_6) δ 26.5 (CH_2), 27.6 ($C(\underline{C}H_3)_3$), 33.9 (CH_2), 59.6 (CH), 59.9 (C_{spiro}), 63.9 (CH_2), 66.4 (C-$\underline{C}H_2$-O), 78.2 ($\underline{C}(CH_3)_3$), 113.0 (CH_{2vin}), 124.0 (CH_{vin}), 131.9 ($\underline{C}H_{vin}$), 138.8 ($\underline{C}H_{vin}$), 152.0 (CO_{Boc}). HRMS (ESI) calcd for $C_{15}H_{23}NO_3Na$ $[M + Na]^+$: 288.1576, found 288.1572.

(2*R*,5*S*)- and (2*S*,5*R*)-7-Oxa-2-vinyl-1-azaspiro[4.5]dec-9-ene Trifluoroacetate Salt (9). To a solution of **8** (55 mg, 0.21 mmol) in CH_2Cl_2 (10 mL), trifluoroacetic acid (0.5 mL) was added. The reaction mixture was stirred at rt for 3 h, and the solvent was removed under reduced pressure. The residue was dissolved in Et_2O (10 mL) and then evaporated. This operation was repeated several times to obtain 52 mg (95%) of a yellow oil corresponding to compound **9**. ^{1}H NMR (400 MHz, D_2O) δ 1.88−1.98 (m, 1H, CH_2), 1.99−2.12 (m, 2H, CH_2), 2.23−2.34 (m, 1H, CH_2), 3.63 (d, 1H, *J* = 12.8 Hz, C-CH_2-O), 4.06 (d, 1H, *J* = 12.8 Hz, C-CH_2-O), 4.14−4.29 (m, 3H, CH + CH_2), 5.40−5.51 (m, 2H, CH_{2vin}), 5.86−5.98 (m, 2H, 2 × CH_{vin}), 6.15−6.22 (m, 1H, CH_{vin}). ^{13}C NMR (100 MHz, D_2O) δ 27.5 (CH_2), 30.3 (CH_2),

59.7 (CH), 61.3 (C_{spiro}), 63.4 (CH_2), 67.1 (C-CH_2-O), 120.6 (CH_{2vin}), 122.3 (CH_{vin}), 129.6 (CH_{vin}), 131.1 (CH_{vin}). HRMS (ESI) calcd for $C_{10}H_{16}NO$ $[M + H]^+$: 166.1226, found 166.1225.

(2*S*,5*S*)- and (2*R*,5*R*)-2-Ethyl-7-oxa-1-azaspiro[4.5]decane Trifluoroacetate Salt (10). A solution of **8** (85 mg, 0.32 mmol) in degassed MeOH (8 mL) was added over a suspension of 10% Pd/C (40 mg) in degassed MeOH (5 mL). The compound **8** was hydrogenated at atmospheric pressure overnight. The reaction mixture was filtered over Celite and evaporated to obtain 85 mg (99%) of a colorless oil. To a solution of this crude in CH_2Cl_2 (10 mL), trifluoroacetic acid (0.5 mL) was added. The reaction mixture was stirred at rt for 3 h, and the solvent was removed under reduced pressure. The residue was dissolved in Et_2O (10 mL) and then evaporated. This operation was repeated several times to obtain 79 mg (93%) of a yellow oil corresponding to compound **10**. ^{1}H NMR (400 MHz, D_2O) δ 1.00 (*t*, 3H, J = 7.5 Hz, CH_3), 1.67−1.79 (m, 4H, CH_2), 1.82−2.00 (m, 4H, CH_2), 2.05−2.15 (m, 1H, CH_2), 2.23−2.33 (m, 1H, CH_2), 3.46−3.53 (m, 1H, O-CH_2), 3.54−3.67 (m, 2H, O-CH_2 + CH), 3.80−3.88 (m, 1H, O-CH_2), 3.89−3.99 (m, 1H, O-CH_2). ^{13}C NMR (100 MHz, D_2O) δ 12.7 ($CH_2\underline{C}H_3$), 24.4 ($\underline{C}H_2CH_3$), 27.2 (CH_2), 30.4 (CH_2), 34.1 (CH_2), 34.5 (CH_2), 63.9 (CH), 67.9 (C_{spiro}), 69.9 (O-CH_2), 72.9 (O-CH_2). HRMS (ESI) calcd for $C_{10}H_{20}NO$ $[M + H]^+$: 170.1539, found 170.1545.

(4*R*,4a*R*,8*R*,10^1*R*)- and (4*S*,4a*S*,8*S*,10^1*S*)-4-Bromo-8-vinylhexahydropyrano[3,4-d]pyrrolo[1,2-*c*]oxazol-6(1*H*)-one (11). To a suspension of **8** (125 mg, 0.47 mmol) in THF (3 mL) and H_2O (2 mL), at 0 °C, NBS (32 mg, 0.56 mmol) was added. After stirring for 7 h, the reaction mixture was diluted with brine. The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The extracts were dried, filtered, and evaporated. The residue was purified by column chromatography, using hexane/EtOAc (1:1) as eluent, to give tricycle **11** (85 mg, 64%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.92−2.02 (m, 1H, CH_2), 2.08−2.19 (m, 2H, CH_2), 2.40−2.51 (m, 1H, CH_2), 3.57 (dd, 1H, J = 12.1, 1.5 Hz, CH_2), 3.89 (d, 1H, J = 12.1 Hz, CH_2), 4.03−4.07 (m, 2H, CH_2), 4.08−4.15 (m, 1H, CH), 4.33−4.37 (m, 1H, CH), 4.60 (d, 1H, J = 2.7 Hz, CH), 5.23−5.31 (m, 2H, CH_{2vin}), 5.78−5.89 (m, 1H, CH_{vin}). ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.9, 34.7 (2 × CH_2), 43.4 (CH), 57.6 (CH), 64.6 (C), 68.4, 72.4 (2 × CH_2), 82.5 (CH), 118.0 (CH_{2vin}), 134.9 (CH_{vin}), 157.1 (CO). HRMS (ESI) calcd for $C_{11}H_{14}BrNO_3$ $[M + H]^+$: 288.0230, $[M + 2 + H]^+$: 290.0210, found 288.0224, 290.0204.

(4*R*,4a*R*,8*R*,10^1*R*)- and (4*S*,4a*S*,8*S*,10^1*S*)-4-Bromo-6-oxooctahydropyrano[3,4-d]pyrrolo[1,2-*c*]oxazole-8-carboxylic Acid (12). A solution of $NaIO_4$ (464 mg, 2.17 mmol) in H_2O (16 mL) was treated with a solution of the substrate **11** (90 mg, 0.31 mmol) in EtOAc/CH_3CN (1:1, 4 mL) followed by $RuCl_3 \cdot H_2O$ (2.6 mg, 0.012 mmol) and $NaHCO_3$ (40 mg). The reaction mixture was stirred vigorously at 30 °C for 2 days. After this time it was extracted into saturated aqueous $NaHCO_3$ (10 mL) and washed with CH_2Cl_2. The aqueous layer was acidified with 2 N HCl to pH 2−3 and extracted with EtOAc (3 × 20 mL). The organic layer was dried with Na_2SO_4 and concentrated in vacuo to provide the carboxylic acid **12** as a white solid (75 mg, 78%). Mp: 120−122 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.00−2.10 (m, 1H, CH_2), 2.20−2.28 (m, 1H, CH_2), 2.45−2.52 (m, 1H, CH_2), 2.57−2.68 (m, 1H, CH_2), 3.55 (dd, 1H, J = 12.1, 1.3 Hz, CH_2), 3.90 (d, 1H, J = 12.1 Hz, CH_2), 4.03 (dd, 1H, J = 13.5, 2.0 Hz, CH_2), 4.12 (dd, 1H, J = 13.0 Hz, CH_2), 4.26 (d, 1H, J = 8.4 Hz, CH), 4.40 (d, 1H, J = 1.3 Hz, CH), 4.94 (s, 1H, CH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.9, 33.8 (2 × CH_2), 42.6 (CH), 56.8 (CH), 63.8 (C), 68.2, 73.0 (2 × CH_2), 83.5 (CH), 156.4, 174.9 (2 × CO). HRMS (ESI) calcd for $C_{10}H_{12}BrNO_5$ $[M + H]^+$: 305.9972, $[M + 2 + H]^+$: 307.9952, found 305.9969, 307.9959.

(2*R*,5*S*)- and (2*S*,5*R*)-(*E*)-3-(1-Boc-7-oxa-1-azaspiro[4.5]-dec-9-ene-2-yl)acrylic Acid Methyl Ester (13). To a solution of **3** (128 mg, 0.48 mmol) and Grubbs second generation catalyst (24 mg, 0.024 mmol) in toluene (15 mL), methyl acrylate (0.44 mL, 4.82 mmol) was added. The reaction was stirred at 80 °C for 16 h, then a second charge of Grubbs second generation catalyst (24 mg, 0.024 mmol) was added, and the reaction was stirred for another 8 h. The solvent was removed under reduced pressure, and the residue was purified by column chromatography using hexane/EtOAc (8:2) as eluent, to give spiro compound **13** (106 mg, 68%) as a colorless oil and compound **8** (23 mg, 18%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.34 (s, 9H, $C(CH_3)_3$), 1.58−1.73 (m, 2H, CH_2), 1.96−2.14 (m, 2H, CH_2), 3.51 (d, 1H, J = 10.3 Hz, O-CH_2), 3.65 (s, 3H, CO_2CH_3), 3.80 (d, 1H, J = 10.3 Hz, O-CH_2), 3.97 (m, 2H, O-CH_2), 4.39−4.48 (m, 1H, CH_2), 5.61−5.72 (m, 2H, 2 × CH_{vin}), 5.78 (dd, 1H, J = 15.7, 1.4 Hz, CH_{vin}), 6.80 (dd, 1H, J = 15.7, 5.6 Hz, CH_{vin}). ^{13}C NMR (100 MHz, DMSO-d_6) δ 26.2 (CH_2), 27.6 ($C(\underline{C}H_3)_3$), 34.1 (CH_2), 50.9 ($CO_2\underline{C}H_3$), 58.8 (C), 60.0 (CH), 63.9 (O-CH_2), 66.6 (O-CH_2), 78.8 (C_{Boc}), 119.4, 124.5, 131.5, 148.5 (4 × CH_{vin}), 165.6 ($\underline{C}O_2CH_3$). HRMS (ESI) calcd for $C_{17}H_{25}NO_5Na$ $[M + Na]^+$: 346.1625, found 346.1633.

(2*R*,5*S*)- and (2*S*,5*R*)-(*E*)-3-(7-Oxa-1-azaspiro[4.5]dec-9-ene-2-yl)acrylic Acid Methyl Ester Trifluoroacetate Salt (14). To a solution of **13** (53 mg, 0.16 mmol) in CH_2Cl_2 (10 mL), trifluoroacetic acid (0.5 mL) was added. The reaction mixture was stirred at rt for 3 h, and the solvent was removed under reduced pressure. The residue was dissolved in Et_2O (10 mL) and then evaporated. This operation was repeated several times to obtain 50 mg (96%) of a yellow oil corresponding to compound **14**. ^{1}H NMR (400 MHz, D_2O) δ 1.89−2.19 (m, 3H, CH_2), 2.30−2.44 (m, 1H, CH_2), 3.64 (d, 1H, J = 12.9 Hz, O-CH_2), 3.75 (s, 3H, CO_2CH_3), 4.06 (d, 1H, J = 12.9 Hz, O-CH_2), 4.12−4.31 (m, 2H, O-CH_2), 4.33−4.44 (m, 1H, CH), 5.90 (dd, 1H, J = 10.2, 1.7 Hz, CH_{vin}), 6.16−6.27 (m, 2H, 2 × CH_{vin}), 6.92 (dd, 1H, J = 15.8, 7.4 Hz, CH_{vin}). ^{13}C NMR (100 MHz, D_2O) δ 31.3 (CH_2), 34.0 (CH_2), 54.8 ($CO_2\underline{C}H_3$), 54.9 (C), 61.2 (CH), 65.8 (O-CH_2), 70.8 (O-CH_2), 125.8, 128.1, 135.5, 142.3 (4 × CH_{vin}), 170.1 ($\underline{C}O_2CH_3$). HRMS (ESI) calcd for $C_{12}H_{18}NO_3$ $[M + H]^+$: 224.1281, found 224.1285.

(2*R*,5*S*)- and (2*S*,5*R*)-(*E*)-3-(7-Oxa-1-azaspiro[4.5]dec-9-ene-2-yl)acrylic Acid Hydrochloride (15). Method A: Compound **13** (26 mg, 0.08 mmol) was dissolved in a mixture of MeOH/H_2O (4:1, 15 mL), and $LiOH \cdot H_2O$ (17 mg, 0.40 mmol) was added. The reaction was stirred at rt for 15 h and was then washed with AcOEt (10 mL). The aqueous layer was acidified with a 2 N HCl solution and extracted with $CHCl_3$/^{i}PrOH 3:1 (3 × 10 mL). The organic layer was dried, filtered, and evaporated to give 22 mg (90%) of a white solid corresponding to an acid, which was used in the following step without purification. This acid was suspended in an aqueous 2 N HCl solution (3 mL) and stirred at room temperature for 24 h. The solvent was evaporated in vacuo at rt. Purification of the residue with C18 reverse-phase sep-pack cartridge gave 17 mg (96%) of a colorless oil corresponding to amino acid derivative **15**. Method B: Compound **13** (23 mg, 0.075 mmol) was suspended in an aqueous 2 N HCl solution (4 mL) and stirred at rt for 5 days. The solvent was evaporated in vacuo at rt. Purification of the residue with C18 reverse-phase sep-pack cartridge gave 17 mg (94%) of a colorless oil corresponding to amino acid hydrochloride **15**. ^{1}H NMR (400 MHz, D_2O) δ 1.98−2.06 (m, 1H, CH_2), 2.07−2.21 (m, 2H, CH_2), 2.36−2.47 (m, 1H, CH_2), 3.70 (d, 1H, J = 12.9 Hz, O-CH_2), 4.11 (dd, 1H, J = 12.9, 1.6 Hz, O-CH_2), 4.19−4.34 (m, 2H, O-CH_2), 4.40−4.49 (m, 1H, CH), 5.92−5.98 (m, 1H, CH_{vin}), 6.19−6.28 (m, 2H, 2 × CH_{vin}), 6.96 (dd, 1H, J = 15.7, 7.4 Hz, CH_{vin}). ^{13}C NMR (75 MHz, D_2O) δ 31.4 (CH_2), 34.0 (CH_2), 61.2 (CH), 65.9 (C), 67.4 (O-CH_2), 70.8 (O-CH_2), 125.8, 128.6, 135.5, 142.7 (4 × CH_{vin}), 171.3 (CO_2H). HRMS (ESI) calcd $C_{11}H_{16}NO_3$ $[M + H]^+$: 210.1125, found 210.1123.

(2*R*,5*S*)- and (2*S*,5*R*)-3-(7-Oxa-1-azaspiro[4.5]decane-2-yl)propanoic Acid Methyl Ester Trifluoroacetate Salt (16). A solution of **13** (58 mg, 0.18 mmol) in degassed MeOH (9 mL) was added over a suspension of 10% Pd/C (18 mg) in degassed MeOH (5 mL). The compound **13** was hydrogenated at atmospheric pressure overnight. The reaction mixture was filtered over Celite and evaporated to obtain 58 mg (99%) of a colorless oil. To a solution of this crude in

CH_2Cl_2 (10 mL), trifluoroacetic acid (0.5 mL) was added. The reaction mixture was stirred at rt for 3 h, and the solvent was removed under reduced pressure. The residue was dissolved in Et_2O (10 mL) and then evaporated. This operation was repeated several times to obtain 55 mg (96%) of a yellow oil corresponding to compound **16**. ^{1}H NMR (400 MHz, D_2O) δ 1.67−1.78 (m, 2H, CH_2), 1.78−1.91 (m, 2H, CH_2), 1.92−2.05 (m, 2H, CH_2), 2.06−2.18 (m, 2H, CH_2), 2.21−2.31 (m, 1H, CH_2), 2.49−2.58 (m, 2H, CH_2), 3.44−3.59 (m, 2H, CH_2), 3.63−3.74 (m, 4H, CH + CO_2CH_3), 3.77-3.84 (m, 1H, CH_2), 3.88−3.96 (m, 1H, CH_2). ^{13}C NMR (100 MHz, D_2O) δ 20.5, 24.9, 26.6, 29.2, 30.3, 30.6 (6 × CH_2), 50.9 ($CO_2\underline{C}H_3$), 57.6 (CH), 64.3 (C), 66.1 (O-CH_2), 69.1 (O-CH_2), 174.0 ($\underline{C}O_2CH_3$). HRMS (ESI) calcd $C_{12}H_{22}NO_3$ $[M + H]^+$: 228.1594, found 228.1591.

(2*R*,5*S*)- and (2*S*,5*R*)-3-(7-Oxa-1-azaspiro[4.5]decane-2-yl)propanoic Acid Hydrochloride (17). Compound **16** (55 mg) was suspended in an aqueous 6 N HCl solution (4 mL) and heated overnight at 100 °C. The solvent was evaporated in vacuo. Purification of the residue with a C18 reverse-phase sep-pack cartridge gave 41 mg (97%) of a colorless oil corresponding to amino acid derivative **17**. ^{1}H NMR (400 MHz, D_2O) δ 1.66−1.77 (m, 2H, CH_2), 1.79−1.90 (m, 2H, CH_2), 1.93−2.04 (m, 2H, CH_2), 2.06−2.19 (m, 2H, CH_2), 2.23−2.32 (m, 1H, CH_2), 2.49−2.58 (m, 2H, CH_2), 3.44−3.58 (m, 2H, CH_2), 3.61−3.75 (m, 2H, CH + CH_2), 3.78−3.85 (m, 1H, CH_2), 3.87−3.96 (m, 1H, CH_2). ^{13}C NMR (100 MHz, D_2O) δ 21.9, 26.3, 28.0, 30.6, 31.7, 32.0 (6 × CH_2), 59.0 (CH), 65.8 (C), 67.5 (O-CH_2), 70.5 (O-CH_2), 176.8 (CO_2H). HRMS (ESI) calcd for $C_{11}H_{20}NO_3$ $[M + H]^+$: 214.1438, found 214.1439.

(2*R*,5*S*)- and (2*S*,5*R*)-1-Boc-2,5-divinylpyrrolidine-2-carboxylic Acid Allyl Ester (18a). A solution of **6a** (85 mg, 0.30 mmol) and [Ru] catalyst (5% mol) in toluene (10 mL) was saturated with ethylene and left under an ethylene atmosphere (1 atm). The mixture was stirred at 80 °C for 14 h. The solvent was removed under reduced pressure, and the residue was purified by column chromatography using hexane/EtOAc (8:2) as eluent, to give pyrrolidine compound **18a** as a colorless oil. [Ru] catalyst: **Ru-1**: 72 mg, 77%; **Ru-2**: 76 mg, 81% and **Ru-3**: 82 mg, 88%.^{1}H NMR (400 MHz, DMSO-d_6, 340 K) δ 1.33 (s, 9H, $C(CH_3)_3$), 1.61−1.74 (m, 1H, CH_2), 2.06−2.20 (m, 3H, CH_2), 4.38−4.51 (m, 1H, CH), 4.52−4.67 (m, 2H, O-CH_2), 5.06 (d, 1H, J = 10.3 Hz, CH_{2vin}), 5.10−5.15 (m, 1H, CH_{2vin}), 5.15−5.26 (m, 3H, CH_{2vin}), 5.34 (dd, 1H, J = 17.3, 1.6 Hz, CH_{2vin}), 5.77−6.00 (m, 2H, 2 × CH_{vin}), 6.36 (dd, 1H, J = 17.4, 10.7 Hz, CH_{vin}). ^{13}C NMR (100 MHz, DMSO-d_6, 340 K) δ 27.6 ($C(\underline{C}H_3)_3$), 32.5 (CH_2), 60.9 (CH), 64.8 ($O\underline{C}H_2$-vinyl), 69.5 (C), 78.8 (C_{Boc}), 112.8, 113.9, 117.2, 117.3, 131.9, 138.8 (3 × CH_{vin} + 3 × CH_{2vin}), 152.5 (CO_{Boc}), 171.5 ($\underline{C}O_2$allyl). HRMS (ESI) calcd for $C_{17}H_{25}NO_4Na$ $[M + Na]^+$: 330.1676, found 330.1685.

(2*R*,5*S*)- and (2*S*,5*R*)-1-Acetyl-2,5-divinylpyrrolidine-2-carboxylic Acid Allyl Ester (18b). A solution of **6b** (25 mg, 0.11 mmol) and Grubbs second generation catalyst (5 mg, 0.006 mmol) in toluene (4 mL) was saturated with ethylene and left under an ethylene atmosphere (1 atm). The mixture was stirred at 80 °C for 14 h. The solvent was removed under reduced pressure, and the residue was purified by column chromatography using hexane/EtOAc (4:6) as eluent, to give pyrrolidine **18b** (20 mg, 73%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.67−1.84 (m, 2H, CH_2), 2.05−2.13 (m, 2H, CH_2), 2.28 (s, 3H, $COCH_3$), 4.40−4.64 (m, 3H, CH + O-CH_2), 5.06−5.28 (m, 6H, 2× CH_{2vin} + CH_{2allyl}), 5.69−5.90 (m, 2H, 2 × CH_{vin}), 6.45 (dd, 1H, J = 17.4, 10.8 Hz, CH_{allyl}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.6 ($CO\underline{C}H_3$), 30.5 (CH_2), 34.8 (CH_2), 62.8 (CH), 65.9 (O-CH_2), 70.7 (C), 113.8, 116.2, 118.1 (2 × CH_{2vin} + CH_{2allyl}), 132.0, 136.5, 138.1 (2 × CH_{vin} + CH_{allyl}), 171.4, 174.6 (CO_{ester}, CO_{amida}). HRMS (ESI) calcd for $C_{14}H_{19}NO_3Na$ $[M + Na]^+$: 272.1257, found 272.1258.

(2*R*,5*S*)- and (2*S*,5*R*)-1-Boc-5-((*E*)-3-methoxy-3-oxoprop-1-enyl)-2-vinylpyrrolidine-2-carboxylic Acid (*E*)-4-Methoxy-4-oxobut-2-enyl Ester (19). To a solution of **6a** (105 mg, 0.38 mmol) and Grubbs second generation catalyst (16 mg, 0.02 mmol) in toluene (12 mL), methyl acrylate (0.34 mL, 3.76 mmol) was added. The reaction was stirred at 80 °C for 16 h, afterward a second charge of Grubbs second generation catalyst (16 mg, 0.02 mmol) was added, and the reaction was stirred for another 8 h. The solvent was removed under reduced pressure, and the residue was purified by column chromatography using hexane/EtOAc (7:3) as eluent, to give spiro compound **19** (98 mg, 62%) as a colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.31 (s, 9H, $C(CH_3)_3$), 1.68−1.79 (m, 1H, CH_2), 2.09−2.25 (m, 3H, CH_2), 3.68 (s, 6H, 2 × CO_2CH_3), 4.53−4.69 (m, 1H, CH), 4.73−4.86 (m, 2H, -CO_2-CH_2), 5.13−5.28 (m, 2H, CH_{2vin}), 5.93 (d, 1H, J = 15.6 Hz, CH_{vin}), 6.06 (d, 1H, J = 15.9 Hz, CH_{vin}), 6.27 (dd, 1H, J = 17.3, 10.8 Hz, CH_{vin}), 6.73−6.96 (m, 2H, 2 × CH_{vin}). ^{13}C NMR (100 MHz, DMSO-d_6) δ 28.3 ($C(\underline{C}H_3)_3$), 29.5, 35.9 (2 × CH_2), 51.8, 51.9 (2 × $CO_2\underline{C}H_3$), 60.5 (CH), 63.8 (-CO_2-CH_2-), 70.5 (C), 80.5 (C_{Boc}), 114.3 (CH_{2vin}), 120.7, 121.6, 121.9, 138.0, 149.1 (5 × CH_{vin}), 166.0, 166.5 (2 × $\underline{C}O_2CH_3$), 172.1 (CO_{ester}). HRMS (ESI) calcd $C_{21}H_{29}NO_8Na$ $[M + Na]^+$: 446.1785, found 446.1772.

(2*R*,5*S*)- and (2*S*,5*R*)-5-((*E*)-3-Methoxy-3-oxoprop-1-enyl)-2-vinylpyrrolidine-5-carboxylic Acid (*E*)-4-Methoxy-4-oxobut-2-enyl Ester Trifluoroacetate Salt (20). To a solution of **19** (35 mg, 0.08 mmol) in CH_2Cl_2 (10 mL), trifluoroacetic acid (0.5 mL) was added. The reaction mixture was stirred at rt for 3 h, and the solvent was removed under reduced pressure. The residue was dissolved in Et_2O (10 mL) and then evaporated. This operation was repeated several times to obtain 33 mg (95%) of a white solid corresponding to compound **20**. Mp: 236−237 °C. ^{1}H NMR (400 MHz, D_2O) δ 2.11−2.22 (m, 1H, CH_2), 2.40−2.50 (m, 1H, CH_2), 2.56−2.64 (m, 1H, CH_2), 2.71−2.80 (m, 1H, CH_2), 3.78 (s, 3H, CO_2CH_3), 3.80 (s, 3H, CO_2CH_3), 4.53−4.62 (m, 1H, CH), 4.98−5.03 (m, 2H, -CO_2-CH_2-), 5.66 (dd, 2H, J = 20.5, 14.1 Hz, CH_{2vin}), 6.07−6.30 (m, 3H, 3 × CH_{vin}), 6.90−7.08 (m, 2H, 2 × CH_{vin}). ^{13}C NMR (100 MHz, $D_2\delta$ 30.6, 34.7 (2 × CH_2), 54.7, 54.9 (2 × $CO_2\underline{C}H_3$), 62.3 (CH), 67.9 (-CO_2-CH_2-), 75.4 (C), 124.2 (CH_{vin}), 124.7 (CH_{2vin}), 128.5, 133.0, 142.2, 143.5 (4 × CH_{vin}), 170.1, 170.8, 171.7 (CO_{ester} + 2 × $\underline{C}O_2CH_3$). HRMS (ESI) calcd $C_{16}H_{22}NO_6$ $[M + H]^+$: 324.1442, found 324.1438.

(2*R*,5*S*)- and (2*S*,5*R*)-1-Boc-7-oxa-2-vinyl-1-azaspiro-[4.5]dec-9-en-6-one (21). Grubbs−Hoveyda catalyst **Ru-3** (13 mg, 0.016 mmol) was added to a solution of **6a** (88 mg, 0.31 mmol) in toluene (9 mL) under argon atmosphere. The mixture was stirred at 80 °C for 14 h. The solvent was removed under reduced pressure, and the residue was purified by column chromatography using hexane/EtOAc (8:2) as eluent, to give spiro compound **21** (35 mg, 41%) as a colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.32 (s, 9H, $C(CH_3)_3$), 1.64−1.73 (m, 1H, CH_2), 1.80−1.91 (m, 1H, CH_2), 2.13−2.23 (m, 2H, CH_2), 4.39−4.52 (m, 1H, CH), 4.82 (d, 1H, J = 16.7 Hz, CH_2-O), 4.87 (d, 1H, J = 16.6 Hz, CH_2-O), 5.09 (dd, 2H, J = 15.2, 13.9 Hz, CH_{2vin}), 5.71−5.80 (m, 1H, CH_{vin}), 5.80−5.90 (m, 1H, CH_{vin}), 5.91−5.97 (m, 1H, CH_{vin}). ^{13}C NMR (100 MHz, DMSO-d_6) δ 27.6 ($C(\underline{C}H_3)_3$), 28.5 (CH_2), 35.7 (CH_2), 60.4 (C_{spiro}), 62.0 (CH), 68.3 ($\underline{C}H_2$-OC=O), 79.1 ($\underline{C}(CH_3)_3$), 113.5 (CH_{2vin}), 134.2, 134.7, 138.9 (3 × CH_{vin}), 154.7 (CO_{Boc}), 170.1 (CO_{ester}). HRMS (ESI) calcd for $C_{15}H_{21}NO_4Na$ $[M + Na]^+$: 302.1363, found 302.1362.

(2*R*,5*S*)- and (2*S*,5*R*)-7-Oxa-2-vinyl-1-azaspiro[4.5]dec-9-en-6-one Trifluoroacetate Salt (22). To a solution of **21** (30 mg, 0.11 mmol) in CH_2Cl_2 (10 mL), trifluoroacetic acid (0.5 mL) was added. The reaction mixture was stirred at rt for 3 h, and the solvent was removed under reduced pressure. The residue was dissolved in Et_2O (10 mL) and then evaporated. This operation was repeated several times to obtain 29 mg of a colorless oil corresponding to compound **22** (96%). ^{1}H NMR (400 MHz, D_2O) δ 2.01−2.13 (m, 1H, CH_2), 2.17−2.38 (m, 2H, CH_2), 2.45−2.56 (m, 1H, CH_2), 4.44−4.55 (m, 1H, CH), 4.96 (dd, 1H, J = 17.5, 3.6 Hz, O-CH_2), 5.07 (d, 1H, J = 17.5 Hz, O-CH_2), 5.36−5.51 (m, 2H, CH_{2vin}), 5.86−5.95 (m, 1H, CH_{vin}), 6.09 (d, 1H, J = 10.2 Hz, CH_{vin}), 6.26 (d, 1H, J = 10.2 Hz, CH_{vin}). ^{13}C NMR (100 MHz,

D_2O) δ 29.3 (CH_2), 37.3 (CH_2), 64.2 (CH), 64.6 (C), 70.3 (O-CH_2), 122.7 (CH_{vin}), 122.8 (CH_{2vin}), 127.0 (CH_{vin}), 131.0 (CH_{vin}), 169.9 (CO_{ester}). HRMS (ESI) calcd for $C_{10}H_{14}NO_2$ $[M + H]^+$: 180.1019, found 180.1019.

(2*S*,5*S*)- and (2*R*,5*R*)-2-Ethyl-7-oxa-1-azaspiro[4.5]decan-6-one Trifluoroacetate Salt (23). A solution of **21** (34 mg, 0.12 mmol) in degassed MeOH (5 mL) was added over a suspension of 10% Pd/C (15 mg) in degassed MeOH (3 mL). The compound was hydrogenated at atmospheric pressure overnight. The reaction mixture was filtered over Celite and evaporated. To a solution of this crude in CH_2Cl_2 (10 mL), trifuoroacetic acid (0.5 mL) was added. The reaction mixture was stirred at rt for 3 h, and the solvent was removed under reduced pressure. The residue was dissolved in Et_2O (10 mL) and then evaporated. This operation was repeated several times to obtain 28 mg (94%) of a colorless oil corresponding to compound **23**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (*t*, 3H, J = 7.5 Hz, CH_3), 1.47−1.65 (m, 2H, CH_2), 1.68−1.97 (m, 4H, CH_2), 2.05−2.24 (m, 3H, CH_2), 2.40−2.49 (m, 1H, CH_2), 3.58−3.68 (m, 3H, CH + CH_2-O). ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.6 (CH_3), 27.5 (CH_2), 29.4 (CH_2), 30.5 (CH_2), 34.9 (CH_2), 36.5 (CH_2), 56.8 (C_{Spiro}), 63.3 (CH_2-O), 65.2 (CH), 177.5 (CO_{ester}). HRMS (ESI) calcd for $C_{10}H_{18}NO_2$ $[M + H]^+$: 184.1332, found 184.1322.

(2*R*,5*S*)- and (2*S*,5*R*)-1-Boc-2-(acryloyloxymethyl)-2,5-divinylpyrrolidine (24). A solution of **4** (82 mg, 0.29 mmol) and Grubbs second generation catalyst (9 mg, 0.015 mmol) in toluene (10 mL) was saturated with ethylene and left under an ethylene atmosphere (1 atm). The mixture was stirred at 80 °C for 14 h. The solvent was removed under reduced pressure, and the residue was purified by column chromatography using hexane/EtOAc (8:2) as eluent, to give pyrrolidine **24** (71 mg, 79%) as a colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6, 340 K) δ 1.33 (s, 9H, $C(CH_3)_3$), 1.52−1.60 (m, 1H, CH_2), 1.99−2.11 (m, 3H, CH_2), 4.29−4.36 (m, 2H, CH + O-CH_2), 4.50 (d, 1H, J = 10.8 Hz, O-CH_2), 4.95−5.08 (m, 3H, CH_{vin} + CH_{2vin}), 5.08−5.16 (m, 2H, CH_{vin} + CH_{2vin}), 5.72−5.82 (m, 1H, CH_{vin}), 5.89−5.93 (m, 1H, CH_{2vin}), 6.15 (d, 1H, J = 10.3 Hz, CH_{vin}), 6.28 (dd, 1H, J = 17.3, 1.6 Hz, CH_{2vin}). ^{13}C NMR (100 MHz, DMSO-d_6, 340 K) δ 27.6 (CH_2), 27.9 ($C(\underline{C}H_3)_3$), 32.5 (CH_2), 57.9 (C), 61.0 (CH), 65.0 (O-CH_2), 78.5 (C_{Boc}), 113.3, 113.6, 127.9, 130.7, 139.2, 139.7 (3 × CH_{vin} + 3 × CH_{2vin}), 152.3 (CO_{Boc}), 164.6 (CO_{ester}). HRMS (ESI) calcd $C_{17}H_{25}NO_4Na$ $[M + Na]^+$: 330.1685, found 330.1676.

(1*R*,4*S*)- and (1*S*,4*R*)-7-Boc-*N*-(prop-1-enyl)-7-azabicyclo-[2.2.1]hept-2-ene-1-carboxamide (25). Compound **25** was obtained from amide **7a** using the same conditions used to obtain spirocyclic compound **8**. The yield was not reproducible. Amide **25** was purified by column chromatography, using hexane/EtOAc (2:8) as eluent. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23−1.29 (m, 1H, CH_2), 1.38 (s, 9H, $C(CH_3)_3$), 1.56−1.63 (m, 5H, CH_2 + CH_3), 2.00−2.07 (m, 1H, CH_2), 2.09−2.17 (m, 1H, CH_2), 4.74−4.78 (m, 1H, CH), 4.80−4.90 (m, 1H, CH_{vin}), 6.30−6.40 (m, 2H, 2 × CH_{vin}), 6.75−6.84 (m, 1H, CH_{vin}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.7 (CH_3), 24.8 (CH_2), 27.9 ($C(\underline{C}H_3)_3$ + CH_2), 62.6 (CH), 74.0 (C), 81.6 ($\underline{C}(CH_3)_3$), 105.2 (CH_{vin}), 121.7 (CH_{vin}), 134.6 (CH_{vin}), 135.6 (CH_{vin}), 155.9 (CO_{Boc}), 167.2 (CO_{amide}). HRMS (ESI) calcd for $C_{15}H_{22}N_2O_3Na$ $[M + Na]^+$: 301.1523, found 301.1524.

(2*R*,5*S*)- and (2*S*,5*R*)-1-Boc-7-benzyl-2-vinyl-1,7-diazaspiro[4.5]dec-9-en-6-one (26). A solution of **7b** (158 mg, 0.43 mmol) and Grubbs second generation catalyst (18 mg, 0.02 mmol) in toluene (12 mL) was saturated with ethylene and left under an ethylene atmosphere (1 atm). The mixture was stirred at 80 °C for 14 h. The solvent was removed under reduced pressure, and the residue was purified by column chromatography using hexane/EtOAc (6:4) as eluent, to give spiro compound **26** (144 mg, 91%) as a colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6, 340 K) δ 1.01−1.45 (m, 9H, $C(CH_3)_3$), 1.53−1.70 (m, 1H, CH_2), 1.81−2.06 (m, 2H, CH_2), 2.27−2.46 (m, 1H, CH_2), 3.71−3.92 (m, 1H, N-CH_2), 4.36−4.64 (m, 2H, CH + N-CH_2), 4.88−5.18 (m, 4H, N-CH_2 + CH_{2vin}), 5.62−5.91 (3 × CH_{vin}), 7.16−7.45 (m, 5H, Ph). ^{13}C NMR (100 MHz, DMSO-d_6, 340 K) δ 28.1 ($C(\underline{C}H_3)_3$), 28.3 (CH_2), 37.7 (CH_2), 42.2 (N-CH_2), 48.2 (N-CH_2), 60.9 (CH), 63.9 (C), 79.3 (C_{Boc}), 113.9 (CH_{2vin}), 128.5, 128.8, 137.7 (3 × CH_{vin}), 153.6 (CO_{Boc}), 169.9 (CO_{amide}). HRMS (ESI) calcd $C_{22}H_{28}N_2O_3Na$ $[M + Na]^+$: 391.1992, found 391.1996.

(2*R*,5*S*)- and (2*S*,5*R*)-7-Benzyl-2-vinyl-1,7-diazaspiro[4.5]-dec-9-en-6-one Trifluoroacetate Salt (27). To a solution of **26** (45 mg, 0.12 mmol) in CH_2Cl_2 (10 mL), trifuoroacetic acid (3 mL) was added. The reaction mixture was stirred at rt for 2 h, and the solvent was removed under reduced pressure, washing several times with Et_2O, obtaining 41 mg (93%) of compound **27** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.09−2.51 (m, 4H, CH_2), 3.83 (s, 2H, CH_2−Ph), 4.42 (*d*, 1H, J = 14.7 Hz, N-CH_2-CH_{vin}), 4.59−4.71 (m, 1H, CH), 4.86 (*d*, 1H, J = 14.2 Hz, N-CH_2-CH_{vin}), 5.31 (*d*, 1H, J = 9.5 Hz, CH_{2vin}), 5.38−5.49 (m, 1H, CH_{2vin}), 5.82−5.92 (m, 1H, CH_{vin}), 5.97−6.11 (m, 1H, CH_{vin}), 6.21−6.29 (m, 1H, CH_{vin}), 7.20−7.39 (m, 5H, Ph). ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.4, 38.8 (2 × CH_2), 47.8 (CH_2-Bn), 50.6 (N-CH_2-CH_{vin}), 64.8 (CH), 65.5 (C), 122.2 (CH_{2vin}), 124.9, 125.3 (2 × CH_{vin}), 128.1, 128.2, 128.6, 128.8, 129.0 (C_{Ph}), 131.6 (CH_{vin}), 166.9 (CO_{amide}). HRMS (ESI) calcd for $C_{17}H_{21}N_2O$ $[M + H]^+$: 269.1648, found 269.1646.

(2*R*,5*S*)- and (2*S*,5*R*)-7-Benzyl-2-ethyl-1,7-diazaspiro[4.5]-decan-6-one Trifluoroacetate Salt (28). A solution of **26** (48 mg, 0.13 mmol) in degassed MeOH (8 mL) was added over a suspension of 10% Pd/C (15 mg) in degassed MeOH (3 mL). The compound was hydrogenated at atmospheric pressure overnight. The reaction mixture was filtered over Celite and evaporated. To a solution of this crude in CH_2Cl_2 (10 mL), trifuoroacetic acid (0.5 mL) was added. The reaction mixture was stirred at rt for 3 h, and the solvent was removed under reduced pressure. The residue was dissolved in Et_2O (10 mL) and then evaporated. This operation was repeated several times to obtain 45 mg (94%) of a colorless oil corresponding to compound **28**. ^{1}H NMR (400 MHz, D_2O) δ 1.00 (*t*, 3H, J = 7.5 Hz, CH_3), 1.70−1.87 (m, 3H, CH_2), 1.95−2.04 (m, 2H, CH_2), 2.14−2.39 (m, 5H, CH_2), 3.34−3.48 (m, 2H, CH_2−N), 3.79−3.88 (m, 1H, CH), 4.36 (*d*, 1H, J = 15.1 Hz, CH_2−Ph), 4.75−4.78 (m, 1H, CH_2−Ph), 7.26−7.32 (m, 2H, C_{Ph}), 7.34−7.44 (m, 3H, C_{Ph}). ^{13}C NMR (100 MHz, D_2O) δ 12.7 (CH_3), 21.4, 27.2, 31.5, 32.9, 38.4 (5 × CH_2), 49.6 (CH_2−N), 53.2 (CH_2−Ph), 67.2 (CH), 70.3 (C), 129.8, 130.1, 131.2, 138.2 (C_{Ph}), 172.0 (CO_{amide}). HRMS (ESI) calcd for $C_{17}H_{25}N_2O$ $[M + H]^+$: 273.1961, found 273.1969.

(2*R*,5*S*)- and (2*S*,5*R*)-1-Boc-2-ethyl-1,7-diazaspiro[4.5]-decan-6-one (29). A solution of **26** (54 mg, 0.15 mmol) in degassed MeOH (8 mL) was added over a suspension of 10% Pd/C (17 mg) in degassed MeOH (3 mL). The compound was hydrogenated at atmospheric pressure overnight. The reaction mixture was filtered over Celite and evaporated. A suspension of this compound (54 mg, 0.14 mmol) in anhydrous ammonia was stirred under argon, and a sufficient amount of sodium to establish a permanent blue coloration was added in portions. The blue solution was stirred for 4 h, and the color was then discharged by addition of the minimum quantity of solid ammonium chloride. The ammonia was allowed to evaporate. The mixture was diluted with H_2O (10 mL) and extracted with EtOAc (3 × 10 mL). The organic layer was dried, filtered, and evaporated. The residue was purified by column chromatography, using CH_2Cl_2/MeOH (95:5) as eluent, to give amide **29** (25 mg, 61%, 2 steps) as a colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.81 (*t*, 3H, J = 7.5 Hz, CH_3), 1.37 (s, 9H, $C(CH_3)_3$), 1.49−1.71 (m, 4H, CH_2), 1.73−1.93 (m, 3H, CH_2), 1.95−2.12 (m, 2H, CH_2), 2.28−2.43 (m, 1H, CH_2), 3.07−3.15 (m, 2H, CH_2−N), 3.73−3.85 (m, 1H, CH), 7.04−7.33 (m, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ 9.8 (CH_3), 20.9 (CH_2), 27.8 ($C(\underline{C}H_3)_3$), 34.9, 37.8, 41.3 (3 × CH_2), 60.4

(CH_2−N), 65.3 (CH), 78.3 (C), 153.1 (CO_{Boc}), 172.7 (CO_{amide}). HRMS (ESI) calcd for $C_{15}H_{26}N_2O_3Na$ $[M + Na]^+$: 305.1836, found 305.1831.

(2*R*,5*S*)- and (2*S*,5*R*)-2-Ethyl-1,7-diazaspiro[4.5]decan-6-one Trifluoroacetate Salt (30). To a solution of **29** (25 mg, 0.12 mmol) in CH_2Cl_2 (10 mL), trifuoroacetic acid (3 mL) was added. The reaction mixture was stirred at rt for 3 h, and the solvent was removed under reduced pressure, washing several times with Et_2O, obtaining 23 mg (95%) of compound **30** as a yellow oil. ^{1}H NMR (400 MHz, D_2O) δ 1.01 (*t*, 3H, J = 7.5 Hz, CH_3), 1.70−1.88 (m, 4H, CH_2), 1.93−2.05 (m, 2H, CH_2), 2.12−2.37 (m, 4H, CH_2), 3.32−3.38 (m, 2H, CH_2−NCO), 3.77−3.86 (m, 1H, CH). ^{13}C NMR (100 MHz, D_2O) δ 12.9 (CH_3), 21.6, 27.5, 31.7, 33.2, 38.5, 43.6 (6 × CH_2), 67.5 (CH), 69.9 (C), 174.1 (CO_{amide}). HRMS (ESI) calcd for $C_{10}H_{19}N_2O$ $[M + H]^+$: 183.1492, found 183.1495.

(2*R*,5*S*)- and (2*S*,5*R*)-1-Boc-7-benzyl-2-ethyl-1,7-diazaspiro-[4.5]decane (31). A solution of **26** (58 mg, 0.16 mmol) in degassed MeOH (8 mL) was added over a suspension of 10% Pd/C (17 mg) in degassed MeOH (3 mL). The compound was hydrogenated at atmospheric pressure overnight. The reaction mixture was filtered over Celite and evaporated. The crude was solved in dry THF (10 mL) and cooled at 0 °C and $LiAlH_4$ (47 mg, 1.25 mmol) was then added. The reaction mixture was heated under reflux overnight under an inert atmosphere. The suspension was cooled and water (5 mL), 10% NaOH (5 mL), and water (5 mL) were added. The mixture was stirred for 30 min, and the product was extracted with ethyl acetate (3 × 15 mL). The combined organic layers were dried, filtered, and evaporated. The residue was purified by column chromatography, using hexane/EtOAc (6:4) as eluent, to give compound **31** (44 mg, 76%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83 (*t*, 3H, J = 7.2 Hz, CH_3), 1.18−1.38 (m, 3H, CH_2), 1.43 (s, 9H, $C(CH_3)_3$), 1.53−1.75 (m, 5H, CH_2), 1.81−2.10 (m, 1H, CH_2), 2.28−2.37 (m, 1H, CH_2), 2.38−2.57 (m, 1H, CH_2), 2.58−2.82 (m, 3H, CH_2), 3.36−3.47 (m, 1H, CH_2), 3.51−3.80 (m, 2H, CH + CH_2), 7.19−7.35 (m, 5H, Ph). ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.2 (CH_3), 23.9, 25.5, 27.7 (3 × CH_2), 28.6 ($C(\underline{C}H_3)_3$), 34.0, 34.6, 53.3, 56.3 (4 × CH_2), 61.3 (CH), 62.7 (CH_2−Ph), 63.5 (C), 78.5 (C_{Boc}), 126.6, 126.7, 128.1, 128.5, 128.6 (C_{Ph}), 153.5 (CO_{Boc}). HRMS (ESI) calcd for $C_{22}H_{35}N_2O_2$ $[M + H]^+$: 359.2693, found 359.2694.

(2*R*,5*S*)- and (2*S*,5*R*)-7-Benzyl-2-ethyl-1,7-diazaspiro[4.5]-decane Trifluoroacetate Salt (32). To a solution of **31** (44 mg, 0.12 mmol) in CH_2Cl_2 (10 mL), trifuoroacetic acid (1 mL) was added. The reaction mixture was stirred at rt for 3 h, and the solvent was removed under reduced pressure, washing several times with Et_2O, obtaining 42 mg (96%) of compound **32** as a yellow oil. ^{1}H NMR (400 MHz, D_2O) δ 0.97 (*t*, 3H, J = 7.2 Hz, CH_3), 1.65−1.95 (m, 5H, CH_2), 1.97−2.38 (m, 5H, CH_2), 3.51−3.66 (m, 2H, CH + CH_2), 4.39 (d, 1H, J = 13.1 Hz, CH_2), 4.48 (d, 1H, J = 13.1 Hz, CH_2), 7.47−7.62 (m, 5H, Ph). ^{13}C NMR (100 MHz, D_2O) δ 10.4 (CH_3), 20.6, 24.9, 28.4, 31.6, 33.5, 52.0, 56.9 (7 × CH_2), 61.6 (CH_2−Ph), 61.9 (CH), 65.5 (C), 129.0, 129.3, 130.7, 130.9, 131.1 (C_{Ph}). HRMS (ESI) calcd for $C_{17}H_{27}N_2$ $[M + H]^+$: 259.2169, found 259.2163.

■ ASSOCIATED CONTENT

Supporting Information. NMR spectra for all new compounds and X-ray data files in CIF format for compounds **7a**, **12**, and **20**. This material is available free of charge via the Internet at http://pubs.acs.org.

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