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Synthesis of nitrogen-containing spirocyclic scaffolds via aminoallylation/RCM sequence

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Abstract—A concise route to nitrogen-containing spirocyclic scaffolds was developed. It is based on the allylation of imines derived from cyclic ketones. The resulting homoallylamines were subsequently alkylated with bromomethylmethacrylate resulting in propenyl-butenyl substituted amine derivatives. Basic amines such as **4** or **10** were cyclized with the Grubbs 2nd generation catalyst in the presence of *p*TsOH. Carbamate derivatives could be converted to tetrahydropiperidine derivatives with the same catalyst. It could be shown that the acrylate functionality can be degraded to the ketone using the classical sequence consisting of Curtius rearrangement of the derived acrylic acid followed by hydrolysis of the vinyl isocyanate. Other modifications include reduction of the acrylate double bond, saponification of the ester group, and amide formation.

1. Introduction

Compound collections or libraries are now commonplace in screening campaigns in industry and academia.[1] The goal can be the discovery of novel cellular targets, novel lead structures,[2] or the optimization of a lead compound. In order to save time and money the hit rate should be high. In this regard compound collections should cover the necessary chemical space in a well balanced manner.[3] Whereas for unbiased screens, broad diversity is desirable, for lead optimization or targeting certain diseases more confined collections might be preferable. Independent of the structural diversity the compounds should have drug-like features or should be natural product-like. Among the various strategies to generate compound collections, the decoration of scaffolds, for example, by automated parallel synthesis is quite common. In chemical terms a scaffold is defined as a mono- or polycyclic structure having several functional groups available for decoration reactions.[4] The design of scaffolds can be inspired by natural products[5] or by the application of novel reactions.[6] As opposed to linear fused or bridged systems, spirocyclic core systems are less common in known drugs and natural products.[7] Some examples of spirocyclic natural products containing a ring nitrogen include cephalotaxine, halichlorine, histrionicotoxin, and manzamine.[8] In the area of non-natural compounds spirocyclic nitrogen-containing systems were fashioned into compounds displaying interesting biological activities.[9] Such spiro scaffolds can be classified according to the ring size of the heterocyclic ring (Fig. 1). A further distinction can be made regarding the position of the nitrogen atom. The other ring can vary in size and the nature of the functional group. Of course, the second ring might be heterocyclic as well. Derived from a parent system **A**, the two pyrrolidine derivatives **A1** and **A2** are conceivable. In the case of the parent system **B**, incorporation of a nitrogen atom into the cyclohexane ring generates the three derived structures **B1**–**B3**.

Some specific examples are illustrated in Figure 2. Frequently one starts with a ring to which the second ring is attached. Eqs. 1,[10] 2,[11] and 3[12] show the formation of a carbocyclic ring by Dieckmann condensation, ring-closing

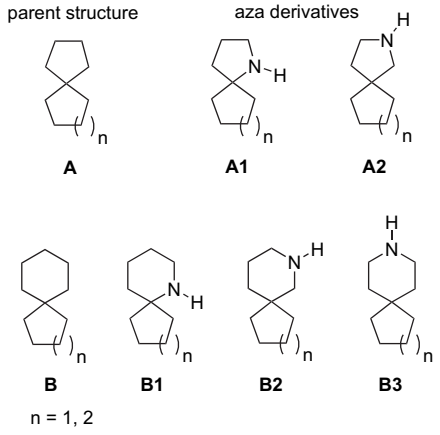

Figure 1. Spirocyclic systems containing at least one ring with a nitrogen atom.

Keywords: Imines; Acrylate; Ring-closing metathesis; Nitrogen-containing heterocycles; Spiro compounds; Scaffolds.
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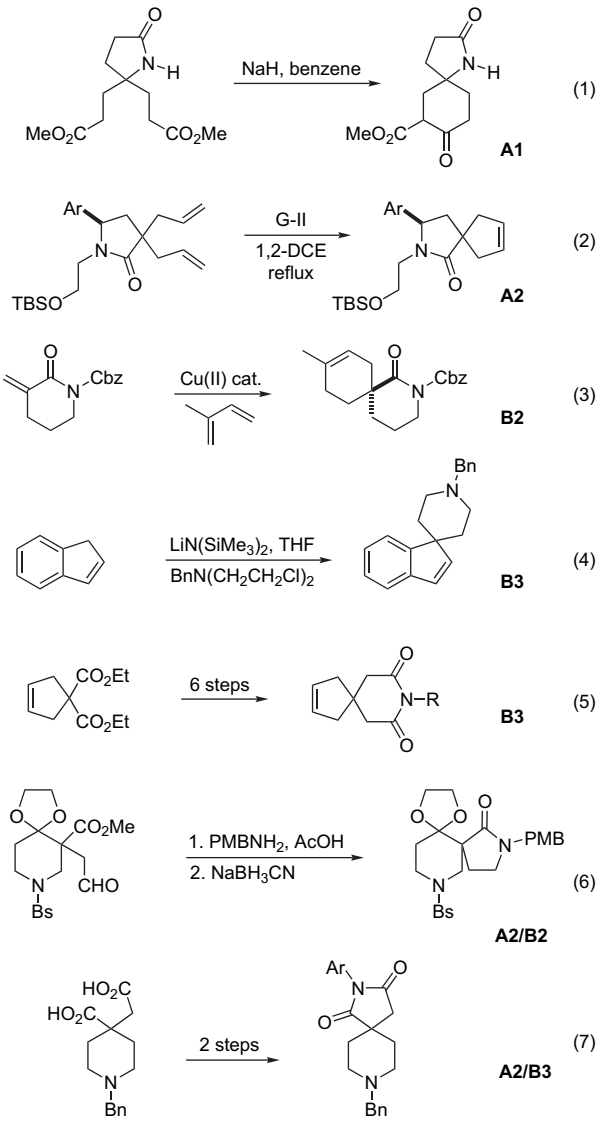


Figure 2. Examples for the synthesis of spirocyclic nitrogen-containing systems.

metathesis, and Diels–Alder reaction, respectively. Eqs. 4[13] and 5[14] demonstrate the formation of the heterocyclic ring. Finally, the formation of diazaspiro compounds is covered in Eqs. 6[15] and 7.[16]

In recent years, the chemistry of spirocyclic systems has flourished due to the advent of multi-component reactions in combination with ring-closing metathesis.[17,18] Some illustrative examples are shown in Figure 3. One interesting case includes the ring-closing metathesis of acryl amides derived from homoallylamines featuring a quaternary center.[19] With these substrates the cyclization required the presence of $Ti(O^iPr)_4$ in order to tame Lewis basic centers. In other work it was shown that cyclic amino ketones can be combined with allylamine and an allyl boronic ester. The resulting diallylamines served as precursors for spirocyclic tetrahydropyridines.[20]

2. Results

We surmised that the versatility of nitrogen-containing spirocyclic ring-closing metathesis would be greatly enhanced

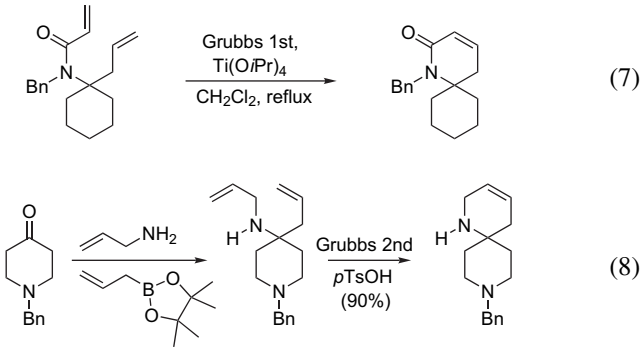
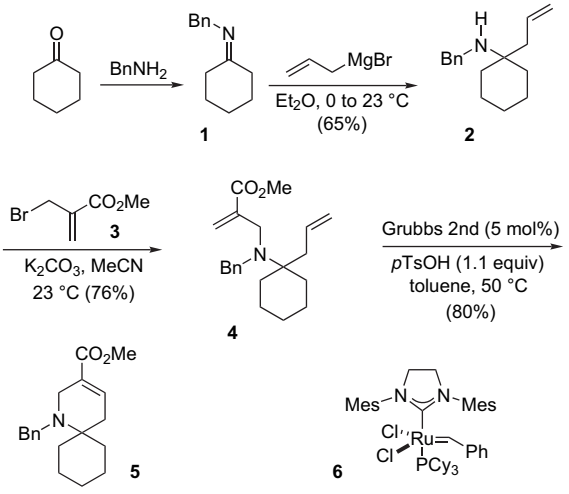


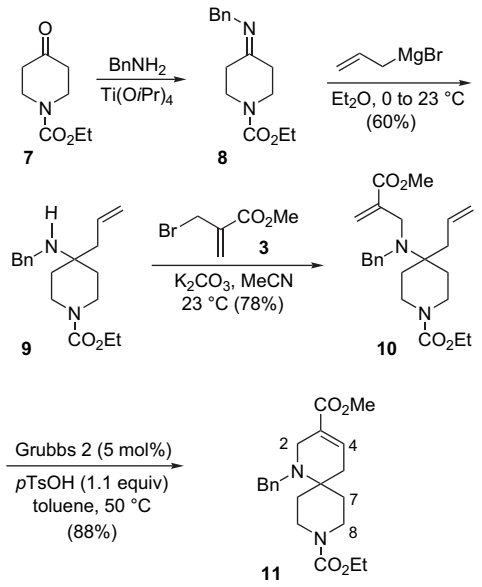
Figure 3. Spirocyclic nitrogen-containing scaffolds via ring-closing metathesis.

if the new double bond would carry some functional group. In this paper, we show that homoallylamines can be reacted with 2-bromomethylacrylate and that a subsequent ring-closing metathesis yields highly functionalized spirocycles.[21] Initial studies were carried out on cyclohexanone (Scheme 1). Thus, cyclohexanone was converted to the corresponding benzylimine **1**. The imine **1** was reacted with allylmagnesium bromide to give the homoallylamine **2** in 65% yield. Stirring of the secondary amine **2** with 2-bromomethylacrylate[22] (**3**) in the presence of potassium carbonate resulted in an allylic substitution. As has been described before, the amine had to be protonated in order for the ring-closing metathesis reaction to succeed. As it turned out the ring-closing metathesis reaction proceeds nicely in the presence of *p*-TsOH (1.1 equiv) and the second generation Grubbs catalyst **6** in toluene at 50 °C. These conditions furnished the tetrahydropyridine derivative **5** in 80% yield. The acrylate proton appears at δ=6.95 ppm in the ^{1}H NMR spectrum.



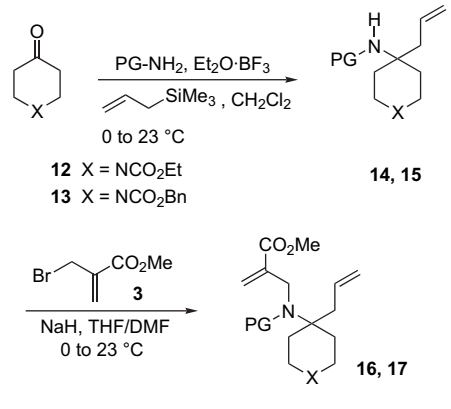
Scheme 1. Preparation of the acrylate derivative **4** and its ring-closing metathesis to the spirocycle **5**.

The same sequence of reactions was also performed with the carbonate protected piperidone **7** (Scheme 2). Accordingly, imine formation with benzylamine in the presence of $Ti(O^iPr)_4$ followed by Grignard addition to the resulting imine **8** furnished the homoallylamine **9**. Allylation with the allyl bromide **3** furnished the diene **10**. Again, the ring-closing metathesis in the presence of *p*-TsOH and the Grubbs catalyst **6** provided the spirocyclic amine **11** in high yield.



Scheme 2. Conversion of the piperidone **7** to acrylate derivative **10** followed by ring-closing metathesis to the spirocyclic diamine derivative **11**.

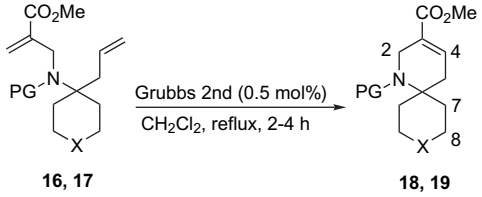
The use of the benzylimines in the above sequence somehow suffered from the moderate yield in the Grignard addition step. Furthermore, due to the basic nature of the compounds chromatographic purification was somewhat difficult. Therefore, it seemed more appropriate to directly prepare nitrogen-protected homoallylamines from the corresponding ketones, a carbamate component, and allylsilane. Thus, using the method of Veenstra and Schmid[23] protected homoallylamines **14a**,**b** and **15a**,**b** were prepared (Scheme 3). The subsequent allylation of the nitrogen atom with 2-bromomethylacrylate **3** required the use of sodium hydride in a THF/DMF mixture. The yields of the alkylation products **16a**,**b** and **17a**,**b** were about 80%.



				yields [%]	
		X	PG	step 1	step 2
14a	**16a**	CH_2	CO_2Bn	88	80
14b	**16b**	CH_2	CO_2Me	90	80
15a	**17a**	NCO_2Et	CO_2Bn	85	80
15b	**17b**	NCO_2Bn	CO_2Me	78	65

Scheme 3. Synthesis of the metathesis substrates **16a**,**b** and **17a**,**b** via addition of allylsilane to intermediate acylimines.

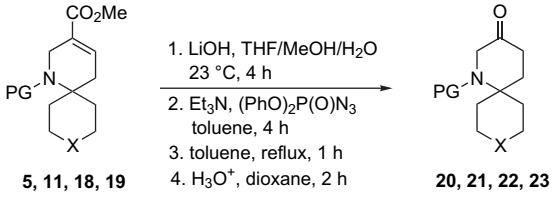
These substrates underwent a smooth ring-closing metathesis reaction in the presence of the Grubbs 2nd generation catalyst **6** (Scheme 4). This way the highly functionalized spiro compounds **18a**,**b** and **19a**,**b** were obtained in yields ranging from 85 to 94%.



		X	PG	yield (%)
16a	**18a**	CH_2	CO_2Bn	90
16b	**18b**	CH_2	CO_2Me	94
17a	**19a**	NCO_2Et	CO_2Bn	85
17b	**19b**	NCO_2Bn	CO_2Me	90

Scheme 4. Formation of the spirocyclic tetrahydropiperidine derivatives **18a**,**b** and **19a**,**b**.

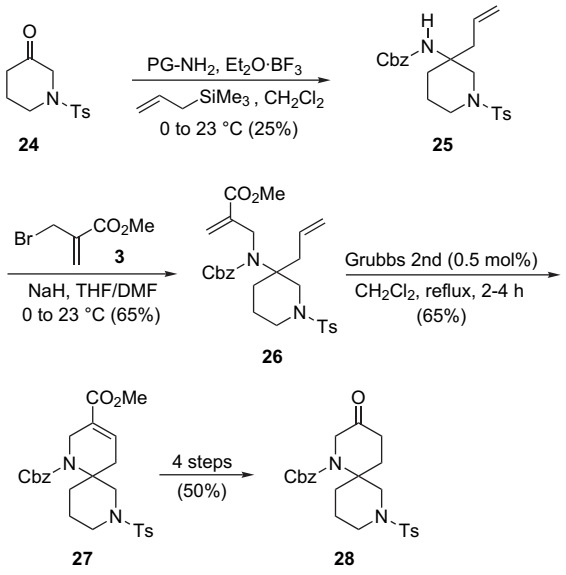
Utilizing a classical sequence, the acrylate function in the metathesis products was converted via ester hydrolysis, Curtius rearrangement, and hydrolysis of the intermediate vinyl isocyanate to the oxopiperidine derivates **20**, **21**, **22a**,**b**, and **23a**,**b** (Scheme 5). Here, the intermediates were not isolated and the overall yields for the four-step sequence were between 60 and 70%. Typically, such 3-piperidinones are fashioned by oxidation of the corresponding alcohols.[24]



		X	PG	yield (%)
5	**20**	CH_2	Bn	70
11	**21**	NCO_2Et	Bn	65
18a	**22a**	CH_2	CO_2Bn	66
18b	**22b**	CH_2	CO_2Me	60
19a	**23a**	NCO_2Et	CO_2Bn	65
19b	**23b**	NCO_2Bn	CO_2Me	63

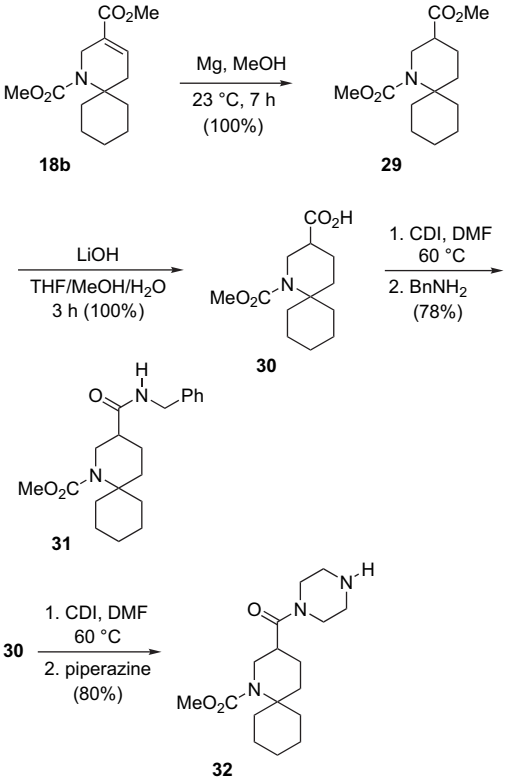
Scheme 5. Conversion of the acrylate to a keto function.

The Veenstra method worked less efficient with 1-toluenesulfonyl-3-piperidinone[25] (**24**). With this substrate, the yield for the protected homoallylamine **25** was rather low (Scheme 6). Most likely, enolization of the aminoketone interferes with the imine formation. Nevertheless, the carbamate **25** could be obtained and converted to the acrylate derivative **26**. The subsequent ring-closing metathesis with the Grubbs 2 catalyst **6** in refluxing dichloromethane provided the desired spirocyclic acrylate **27** in 65% yield. As described in Scheme 6 degradation of the acrylate functionality via Curtius rearrangement led to the ketone **28** featuring two differently protected amino functions.



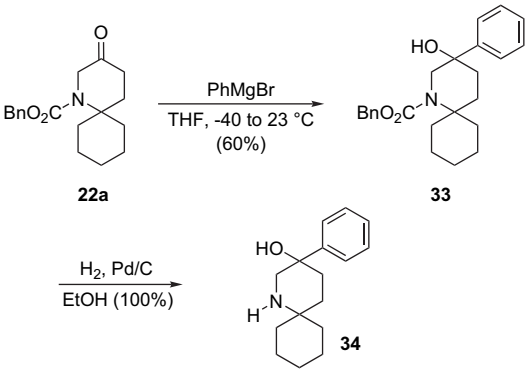
Scheme 6. Synthesis of the spirocyclic ketone **28**.

The acrylate function in the spirocycles offers other possibilities for derivatization. For example, reductive removal of the double bond on compound **18b** using magnesium in methanol[26] afforded the saturated ester **29** in quantitative yield (Scheme 7). Saponification gave the carboxylic acid **30**. With this acid, amide formation was illustrated. Thus, activation of the acid with carbonyl diimidazole and treatment with benzylamine and piperazine, respectively, gave amides **31** and **32**.



Scheme 7. Conjugate reduction of the acrylate double bond of **18b**, ester saponification, and condensation reactions of the acid **30** with some amines.

The keto function obtained from degradation of the α,β-unsaturated ester presents itself for addition reactions with organometallic nucleophiles. To investigate this pathway, ketone **22a** was treated with phenylmagnesium bromide in THF at −40 °C. After warming to room temperature and aqueous workup, the tertiary alcohol **33** was obtained (Scheme 8). We note that this compound contains a β-phenylethylamine substructure, although in protected form. Hydrogenolytic removal of the Cbz protecting group provided the secondary amine **34**.



Scheme 8. Addition reactions to the ketone **22a**.

3. Conclusion

In summary, we described the facile formation of spirocyclic amine derivatives via alkene ring-closing metathesis. Unlike with many other RCM substrates one of the double bonds is part of a 2-methylacrylate subunit. In this way the ring-closing reaction yields tetrahydro-3-pyridinecarboxylates, connected to another ring via a common atom. The substrates for the ring-closing metathesis are easily available from cyclic ketones via imine formation followed by nucleophilic allylation. Alkylation of the nitrogen atom with the 2-bromomethylacrylate **3** gave the substrates for the ring-closing metathesis reaction. Degradation of the α,β-unsaturated ester via Curtius rearrangement and hydrolysis led to keto derivatives. In order to illustrate the potential of the RCM products as scaffolds, functionalization reactions were performed on the ester **18b** and the ketone **22a**.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR: Bruker Avance 400, spectra were recorded at 295 K in $CDCl_3$. Chemical shifts are calibrated to the residual proton and carbon resonance of the solvent: $CDCl_3$ (δ_H 7.25, δ_C 77.0 ppm). Melting points: Büchi Melting Point B-540, uncorrected. IR: Jasco FTIR-430. EIMS: Finnigan Triple-Stage-Quadrupol (TSQ-70). HRMS (FTICR): Bruker Daltonic APEX 2 with electron spray ionization (ESI). Analytical LC–MS: HP 1100 Series connected with an ESIMS detector Agilent G1946C, positive mode with fragmentor voltage of 40 eV; column: Nucleosil 100-5, C-18 HD, 5 mm, 70×3 mm Macherey–Nagel; eluent: NaCl solution (5 mM)/acetonitrile, gradient: 0–10–15–17–20 min with

20–80–80–99–99% acetonitrile, flow: 0.5 mL/min. Flash chromatography: J. T. Baker silica gel 43–60 μm. Thin-layer chromatography: Macherey–Nagel Polygram Sil G/UV_{254}. Solvents were distilled prior to use; petroleum ether with a boiling range of 40–60 °C was used. Reactions were generally run under an argon atmosphere. All operations with Grubbs second generation catalyst must be done in glow-box or dry-box. *N*-(Benzyl)-1-prop-2-en-1-ylcyclohexanamine (**2**) was prepared according to the literature.[19]

4.1.1. General procedure 1 for the carbamino allylation of cyclic ketones (GP1). To a cooled (0 °C) solution of the ketone (10 mmol), the carbaminic acid ester (12 mmol), and allyltrimethylsilane (14 mmol, 2 mL) in CH_2Cl_2 (10 mL), freshly distilled $BF_3 \cdot Et_2O$ (1.70 g, 12.0 mmol, 1.52 mL) was slowly added dropwise over 3 min with vigorous stirring. Then, the reaction mixture was stirred for 1 h at 0 °C and 8 h at room temperature. At this point approximately 80% conversion was usually achieved. The reaction was quenched with saturated $NaHCO_3$ solution (10 mL) followed by separation of the layers. The organic layer was dried over Na_2SO_4, filtered, and evaporated to dryness. The residue was resubjected for the same reaction, but this time with a 30% load of carbamate, allylsilane, and $BF_3 \cdot Et_2O$ (namely 3.6 mmol of ester, 4.2 mmol of silane, and 3.6 mmol of $BF_3 \cdot Et_2O$), to produce almost complete conversion. Crude material used further without purification.

4.1.2. General procedure 2 for the alkylation of the carbamates with bromomethylmethacrylate (GP2). A suspension of NaH (60% in mineral oil, 800 mg, 20 mmol, 2 equiv) was washed twice with abs THF, and then re-suspended in a mixture of THF/DMF (2 mL/3 mL, respectively). To this suspension at 0 °C was added the corresponding carbamate (10 mmol) in THF (2 mL) with vigorous stirring over 5 min. Then, the reaction mixture was stirred at 0 °C for 30 min, before bromomethylmethacrylate (3.6 g, 2.0 mL, 2 equiv) was added over 5 min. The reaction mixture was stirred for 1 h at 0 °C, and then allowed to stir overnight with concomitant warming to room temperature. Thereafter, the mixture was poured into a stirred mixture of saturated NH_4Cl solution/Et_2O (20 mL/20 mL). After separation of the layers, the water phase was extracted with Et_2O (10 mL). The combined organic layers were washed with saturated NaCl solution (20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (toluene/Et_2O mixtures).

4.1.3. General procedure 3 for the ring-closing metathesis (RCM) of *N*-carbamate protected amines (GP3). A solution of diene in abs CH_2Cl_2 (3 mL/mmol) was degassed by bubbling N_2 or Ar through it, and then transferred into a two neck flask (25 mL), equipped with reflux condenser and attached to a vacuum inert gas line. The flask was carefully purged with inert gas three times, then second generation Grubbs catalyst (0.5 mol %, 4.4 mg/mmol) was added, and the reaction mixture was refluxed for 4 h. The reaction progress can be monitored by TLC. After completion of the reaction, the solvent was evaporated and the residue subjected to flash chromatography (toluene/Et_2O).

4.1.4. General procedure 4 for the preparation of imines from cyclic ketones and benzylamine (GP4). A mixture of benzylamine (12 mmol), the cyclic ketone (10 mmol), and 4 Å molecular sieves in toluene (25 mL) was slowly stirred for 24 h. Thereafter, the molecular sieves were filtered off and washed with toluene. The combined filtrates were concentrated in vacuo. The crude benzylimines were used without further purification.

4.1.5. General procedure 5 for the addition of allylmagnesium to benzylimines (GP5). To a solution of *N*-benzylimine (10 mmol) in dry Et_2O (20 mL, 2 mL/mmol of imine) was added dropwise a solution of allylmagnesium bromide (10 mL, 2 M in Et_2O, 20 mmol) at 0 °C with vigorous stirring. Stirring was continued for 1 h at 0 °C and 3 h at room temperature. The reaction was quenched with saturated ammonium chloride solution. The layers were separated and the aqueous layer was extracted with Et_2O (2×10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The obtained residue was purified by flash chromatography.

4.1.6. General procedure 6 for the alkylation of *N*-benzylamines (GP6). To a solution of the amine **2** or **9** (6 mmol) in acetonitrile (20 mL, 3 mL/mmol) was added finely powdered potassium carbonate (1.78 g, 12.0 mmol, 2 equiv) and then bromomethylmethacrylate (7.2 mmol, 1.2 g, 0.7 mL, 1.2 equiv) in acetonitrile (2 mL). This mixture was stirred overnight, filtered, and the filter cake washed with acetonitrile. The combined filtrates were evaporated and the residue purified by flash chromatography.

4.1.7. General procedure 7 for the RCM of the *N*-benzyl protected dienes (GP7). To a degassed solution of the diene in toluene (10 mL/mmol) was added TsOH monohydrate (1.1 equiv) followed by heating of the mixture to 50 °C for 30 min. Then, the second generation Grubbs catalyst (5 mol %) was added and the mixture stirred for 4 h at 55 °C. Then, saturated Na_2CO_3 solution (2 mL/mmol) was added and the resulting mixture filtered through a pad of Celite. The layers of the filtrate were separated. The organic phase was dried over Na_2SO_4, filtered, and evaporated. The crude product was purified by flash chromatography (toluene/Et_2O).

4.1.8. General procedure 8 for the degradation of the unsaturated esters to ketones (GP8). To a solution of the unsaturated ester in a mixture of THF/MeOH/H_2O (3:2:1, v/v/v, 6 mL/mmol) was added LiOH (5 equiv) and the mixture stirred at room temperature for 3 h. Then, saturated NH_4Cl solution (1 mL/mmol) was added, and most of the organic solvents removed in vacuo. The partly solid residue was extracted with CH_2Cl_2 (3×10 mL/mmol), dried with Na_2SO_4, filtered, and concentrated in vacuo. The obtained residue was dissolved in toluene (5 mL/mmol), followed by the addition of triethylamine (3 equiv) and diphenylphosphorylazide (1.2 equiv). After stirring the mixture for 5 h at room temperature, it was filtered through a pad of SiO_2 (flash silica gel, 2 cm). The silica gel was additionally washed with toluene (10 mL). The filtrate was then refluxed for 1 h. The solution containing the rearranged isocyanate was evaporated and the residue taken up in dioxane (5 mL/mmol). To this solution 1 N HCl was added (1 mL/mmol) and the mixture stirred for 2 h at room temperature. Thereafter, the mixture was concentrated in vacuo and the obtained residue purified by flash chromatography.

4.2. Methyl 2-{[(benzyl)(1-prop-2-en-1-ylcyclohexyl)-amino]methyl}prop-2-enoate (4)

Prepared according to GP6, yield 3.0 g (76%); R_f (Et_2O/toluene, 1:3): 0.67; ^1H NMR (400 MHz, $CDCl_3$): δ=1.11–1.75 (m, 10H, CH_2), 2.31 (d, J=7.3 Hz, 2H, H_2C=CHCH_2), 3.42 (s, 2H, NCH_2), 3.51 (s, 3H, CO_2CH_3), 3.70 (s, 2H, $PhCH_2$), 4.89–5.02 (m, 2H, H_2C=), 5.67 (s, 1H (H_2C=C(CO_2Me), E)), 5.84 (s, 1H (H_2C=C(CO_2Me), Z)), 5.95 (ddt, J=17.0, 10.0, 7.6 Hz, 1H, H_2C=CHCH$_2$), 7.12 (t, J=7.3 Hz, 2H, CH_{ar}, *para*), 7. 21 (t, J=7.3 Hz, 2H, CH_{ar}, *meta*), 7.28 (d, J=7.3 Hz, 2H, CH_{ar}, *ortho*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=22.6 (CH_2), 26.4 (CH_2), 33.4 (CH_2), 38.3 (H_2C=C(CO_2-Me)CH_2), 49.8 (H_2C=CHCH_2), 51.8 (CO_2CH_3), 54.0 ($PhCH_2$), 60.4 (C_{quat}), 117.2 (H_2C=CH), 126.7 (H_2C=C(CO_2Me)), 126.8 (CH_{ar}, *ortho*, *para*), 128.9 (CH_{ar}, *ortho*), 129.2 (CH_{ar}, *meta*), 136.1 (H_2C=CHCH$_2$), 139.3 (H_2C=C(CO_2Me)), 142.2 (C_{ar}), 167.8 (CO_2Me); HRMS (EI): calcd for $C_{21}H_{30}NO_2$ $[M+H]^+$ 328.22711, found 328.22710.

4.3. Methyl 1-(benzyl)-1-azaspiro[5.5]undec-3-ene-3-carboxylate (5)

Prepared according to GP7, yield 160 mg (80%); white crystals, mp 117–119 °C; R_f (Et_2O/toluene, 1:3): 0.53; ^1H NMR (400 MHz, $CDCl_3$): δ=1.19–1.37 (m, 5H, CH_2), 1.45–1.56 (m, 1H, CH), 1.63–1.77 (m, 4H, CH_2), 1.98–2.05 (m, 2H, 5-H), 3.21 (s, 2H, 2-H), 3.49 (s, 2H, $PhCH_2$), 3.56 (s, 3H, CO_2CH_3), 6.93–6.98 (m, 1H, CH=C(CO_2Me)), 7.12 (t, J=7.3 Hz, 2H, CH_{ar}, *para*), 7. 21 (t, J=7.3 Hz, 2H, CH_{ar}, *meta*), 7.28 (d, J=7.3 Hz, 2H, CH_{ar}, *ortho*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=21.3 (C-8), 26.5 (C-9), 32.6 (C-5), 34.6 (C-7), 44.0 (C-2), 50.3 ($PhCH_2$), 51.3 (CO_2CH_3), 53.1 (C_{quat}), 126.4 (CH_{ar}, *para*), 127.4 (HC=*C*(CO_2Me)), 128.1 (CH_{ar}, *ortho*, *meta*), 137.7 (CH=C(CO_2Me)), 140.9 (C_{ar}), 166.9 (CO_2Me); HRMS (EI): calcd for $C_{19}H_{26}NO_2$ $[M+H]^+$ 300.19581, found 300.19563.

4.4. Ethyl 4-[(benzyl)amino]-4-prop-2-en-1-ylpiperidine-1-carboxylate (9)

To a mixture of *N*-carbethoxy-4-piperidone (**7**) (1.14 g, 6.7 mmol) and benzylamine (0.8 g, 0.8 mL, 7.3 mmol, 1.1 equiv) was added titanium tetraisopropoxide (4 mL, 13.4 mmol, 2 equiv) with vigorous stirring. After 4 h at room temperature, vacuum was applied to the flask and kept for 15 min at 1 mbar. The resulting viscous oil was dissolved with Et_2O (35 mL). Then, allylmagnesium bromide (7 mL, 1 M in Et_2O) was added dropwise over 15–30 min followed by stirring the mixture overnight at room temperature. The mixture was diluted with additional Et_2O (30 mL), poured into saturated aqueous NH_4Cl solution (30 mL), and stirred for 30 min. Then, the two-phase mixture was filtered through a pad of Celite. After separation of the layers, the aqueous layer was extracted with Et_2O (2×30 mL). The combined organic layers were washed with saturated NaCl solution, dried over Na_2SO_4, filtered, and evaporated. The residue was purified by flash chromatography, yield 1.2 g (60%); R_f (Et_2O/toluene, 1:3): 0.64; ^1H NMR (400 MHz, $CDCl_3$): δ=1.17 (t, J=7.1 Hz, 3H, CH_3CH$_2$O), 1.32–1.58 (m, 4H, 3,5-H), 2.19 (d, J=7.3 Hz, 2H, H_2C=CHCH_2), 3.21–3.34 (m, 2H, 2,6-H), 3.53–3.80 (m, 2H, 2,6-H), 3.57 (s, 2H, $PhCH_2$), 4.04 (q, J=7.2 Hz, 2H, CH_3CH_2O), 5.02–5.11 (m, 2H, H_2C=CHCH_2), 5.73 (ddt, J=17.0, 10.0, 7.6 Hz, 1H, H_2C=CHCH$_2$), 7.12–7.32 (m, 5H, CH_{ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.6 (CH_3CH$_2$O), 34.6 (C-3,5), 39.4 (C-2,6), 42.2 (H_2C=CHCH_2), 45.3 ($PhCH_2$), 52.5 (C-4), 61.0 (CH_3CH_2O), 118.5 (H_2C=CHCH$_2$), 126.8 (CH_{ar}, *para*), 128.1 (CH_{ar}, *ortho*), 128.3 (CH_{ar}, *meta*), 133.0 (H_2C=*C*HCH$_2$), 140.9 (C_{ar}), 155.6 (CO_2Et).

4.5. Ethyl 4-[{2-[(methyloxy)carbonyl]prop-2-en-1-yl}-(benzyl)amino]-4-prop-2-en-1-ylpiperidine-1-carboxylate (10)

Prepared according to GP6, yield 1.1 g (78%); R_f (Et_2O/toluene, 1:3): 0.56; ^1H NMR (400 MHz, $CDCl_3$): δ=1.14 (t, J=7.2 Hz, 3H, CH_3CH_2O), 1.44–1.74 (m, 4H, $C_{quat}CH_2$), 2.32 (d, J=7.3 Hz, 2H, H_2C=CHCH_2), 3.14–3.25 (m, 2H, NCH_2), 3.41–3.45 (m, 2H, H_2C=C(CO_2Me)CH_2), 3.48–3.58 (m, 2H, NCH_2), 3.56 (s, 3H, CO_2CH_3), 3.70 (s, 2H, $PhCH_2$), 4.01 (q, J=7.2 Hz, 2H, CH_3CH_2O), 4.97–5.06 (m, 2H, H_2C=CHCH$_2$), 5.56–5.58 (m, 1H (H_2C=C(CO_2Me), E)), 5.80–5.93 (m, 2H, H_2C=CHCH$_2$ (H_2C=C(CO_2Me), Z)), 7.02–7.14 (m, 5H, CH_{ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.6 (CH_3CH$_2$O), 32.5 ($C_{quat}CH_2$), 37.7 (H_2C=C(CO_2Me)CH_2), 39.8 (NCH_2), 50.0 (H_2C=CHCH_2), 51.5 (CO_2CH_3), 53.5 ($PhCH_2$), 58.6 (C_{quat}), 61.0 (CH_3CH_2O), 119.2 (H_2C=CHCH$_2$), 126.5 (CH_{ar}, *para*), 126.7 (H_2C=C(CO_2Me)), 127.9 (CH_{ar}, *ortho*), 128.4 (CH_{ar}, *meta*), 134.5 (H_2C=*C*HCH$_2$), 139.3 (H_2C=*C*(CO_2Me)), 141.0 (C_{ar}),155.4 (NCO_2Et), 167.2 (H_2C=C(*C*O_2Me)); HRMS (EI): calcd for $C_{23}H_{33}N_2O_4$ $[M+H]^+$ 401.24348, found 401.24341.

4.6. 9-Ethyl 3-methyl-1-(benzyl)-1,9-diazaspiro[5.5]-undec-3-ene-3,9-dicarboxylate (11)

Prepared according to GP7, yield 240 mg (88%); R_f (Et_2O/toluene, 1:1): 0.61; ^1H NMR (400 MHz, $CDCl_3$): δ=1.19 (t, J=7.1 Hz, 3H, CH_3CH$_2$O), 1.31–1.43 (m, 2H, 7,11-H), 1.78–1.91 (m, 2H, 7,11-H), 2.04–2.11 (m, 2H, 5-H), 3.25 (s, 2H, 2-H), 3.37–3.47 (m, 2H, 8,10-H), 3.51 (s, 2H, $PhCH_2$), 3.54–3.70 (m, 2H, 8,10-H), 3.61 (s, 3H, CO_2CH_3), 4.07 (q, J=7.1 Hz, 2H, CH_3CH_2O), 6.97–7.02 (m, 1H, CH=C(CO_2Me)), 7.13–7.30 (m, 5H, CH_{ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.7 (CH_3CH$_2$O), 31.9 (C-5), 33.9 (C-7,11), 39.1 (C-8,10), 44.2 (C-2), 50.4 ($PhCH_2$), 51.5 (CO_2CH_3), 51.9 (C-6), 61.2 (CH_3CH_2O), 126.8 (CH_{ar}, *para*), 127.4 (C-3), 128.0 (CH_{ar}, *meta*), 128.4 (CH_{ar}, *ortho*), 137.0 (C-4), 140.0 (C_{ar}), 155.7 (NCO_2Et), 166.7 (CO_2Me); HRMS (EI): calcd for $C_{21}H_{29}N_2O_4$ $[M+H]^+$ 373.21218, found 373.21192.

4.7. Benzyl (1-prop-2-en-1-ylcyclohexyl)carbamate (14a)

Prepared according to GP1, yield 2.4 g (88%), slightly green oil; R_f (Et_2O/toluene, 1:1): 0.78; ^1H NMR (400 MHz, $CDCl_3$): δ=1.10–1.55 (m, 8H, 4CH_2), 1.70–2.00 (m, 2H, CH_2), 2.40 (d, J=7.3 Hz, 2H, H_2C=CHCH_2), 4.46 (s, 1H, NH), 4.89–5.02 (m, 4H, $PhCH_2$, H_2C=), 5.68 (ddt, J=17.0, 10.0, 7.6 Hz, 1H, H_2C=CHCH$_2$), 7.20–7.32 (m, 5H, CH_{ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ=22.0 (CH), 26.0 (CH_2), 34.7 (CH_2), 42.9 (H_2C=CHCH_2), 55.1 (C_{quat}), 66.4 ($PhCH_2$), 118.5 (H_2C=CH), 128.4 (CH_{ar}, *ortho*, *para*),

128.9 (CH_{ar}, *meta*), 134.1 ($H_2C{=}CHCH_2$), 137.3 (C_{ar}), 154.9 (C=O); HRMS (EI): calcd for $C_{20}H_{42}O_2Si_2Na$ $[M+Na]^+$ 393.26155, found 393.26159.

4.8. Methyl (1-prop-2-en-1-ylcyclohexyl)carbamate (14b)

Prepared according to GP1, yield 1.77 g (90%), slightly green oil; R_f (Et_2O/toluene, 1:1): 0.75; ^1H NMR (400 MHz, $CDCl_3$): δ=1.15–1.60 (m, 8H, $4CH_2$), 1.80–2.00 (m, 2H, CH_2), 2.43 (d, J=7.1 Hz, 2H, $H_2C{=}CHCH_2$), 3.59 (s, 3H, OCH_3), 4.45 (s, 1H, NH), 4.97–5.08 (m, 2H, $H_2C{=}$), 5.73 (ddt, J=17.0, 10.0, 7.6 Hz, 1H, $H_2C{=}CHCH_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ=21.5 (CH_2), 25.6 (CH_2), 34.7 (CH_2), 42.5 ($H_2C{=}CHCH_2$), 51.4 (OCH_3), 54.5 (C_{quat}), 66.4 ($PhCH_2$), 117.9 ($H_2C{=}CH$), 133.7 ($H_2C{=}CHCH_2$), 155.2 (C=O).

4.9. Ethyl 4-({[(benzyl)oxy]carbonyl}amino)-4-prop-2-en-1-ylpiperidine-1-carboxylate (15a)

Prepared according to GP1, yield 2.15 g (85%), slightly yellow oil; R_f (Et_2O/toluene, 1:1): 0.64; ^1H NMR (400 MHz, $CDCl_3$): δ=1.23 (t, J=7.1 Hz, 3H, CH_3CH_2O), 1.43–1.55 (m, 2H, CH_2), 1.90–2.10 (m, 2H, CH_2), 2.36–2.56 (m, 2H, $H_2C{=}CHCH_2$), 2.96–3.19 (m, 2H, CH_2N), 3.68–3.97 (m, 2H, CH_2N), 4.10 (q, J=7.1 Hz, 2H, CH_3CH_2O), 4.64 (s, 1H, NH), 4.97–5.17 (m, 4H, $PhCH_2$, $H_2C{=}CH$), 5.70 (ddt, J=17.0, 10.0, 7.6 Hz, 1H, $H_2C{=}CHCH_2$), 7.27–7.37 (m, 5H, CH_{ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.6 (CH_3), 34.0 (CH_2), 39.4 (CH_2N), 42.3 ($H_2C{=}CHCH_2$), 53.2 (C_{quat}), 61.2 (CH_3CH_2O), 66.2 ($PhCH_2$), 119.0 ($H_2C{=}CH$), 128.0 (CH_{ar}, *ortho*), 128.1 (CH_{ar}, *para*), 128.5 (CH_{ar}, *meta*), 132.5 ($H_2C{=}CHCH_2$), 136.4 (C_{ar}), 154.6 (CO_2Bn), 155.4 (CO_2Et).

4.10. Benzyl 4-{[(methyloxy)carbonyl]amino}-4-prop-2-en-1-ylpiperidine-1-carboxylate (15b)

Prepared according to GP1, yield 2.6 g (78%), slightly yellow oil; R_f (Et_2O/toluene, 1:1): 0.52; ^1H NMR (400 MHz, $CDCl_3$): δ=1.41–1.55 (m, 2H, CH_2), 1.90–2.10 (m, 2H, CH_2), 2.37–2.48 (m, 2H, $H_2C{=}CHCH_2$), 2.96–3.19 (m, 2H, CH_2), 3.60 (s, 3H, OCH_3), 3.71–3.97 (m, 2H, CH_2), 4.50 (s, 1H, NH), 4.97–5.17 (m, 4H, $PhCH_2$, $H_2C{=}$), 5.68 (ddt, J=17.0, 10.0, 7.6 Hz, 1H, $H_2C{=}CHCH_2$), 7.22–7.37 (m, 5H, CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ=34.5 (CH_2), 40.0 (CH_2N), 42.8 ($H_2C{=}CHCH_2$), 55.1 (C_{quat}), 53.5 (CH_3O), 67.5 ($PhCH_2$), 119.5 ($H_2C{=}CH$), 128.3 (CH_{ar}, *ortho*), 128.4 (CH_{ar}, *para*), 128.9 (CH_{ar}, *meta*), 133.0 ($H_2C{=}CHCH_2$), 137.2 (C_{quat}), 155.6 (CO_2Bn), 155.8 (CO_2Me).

4.11. Methyl 2-{[{[(benzyl)oxy]carbonyl}(1-prop-2-en-1-ylcyclohexyl)amino]methyl}prop-2-enoate (16a)

Prepared according to GP2, yield 2.5 g (80%), colorless oil; R_f (Et_2O/toluene, 1:1): 0.88; ^1H NMR (400 MHz, $CDCl_3$) δ=1.04–1.57 (m, 8H, CH_2), 2.17–2.29 (m, 2H, CH_2), 2.65 (d, J=7.3 Hz, 2H, $H_2C{=}CHCH_2$), 3.69 (s, 3H, CO_2CH_3), 4.01 (s, 2H, $H_2C{=}C(CO_2Me)CH_2$), 4.87–5.04 (m, 4H, $PhCH_2$, $H_2C{=}$), 5.54–5.72 (m, 2H, $H_2C{=}CHCH_2$ ($H_2C{=}C(CO_2Me)$, *E*)), 7.17–7.35 (m, 5H, CH_{ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ=22.7 (CH_2), 25.4 (CH_2), 34.1 ($C_{quat}CH_2$), 36.7 ($H_2C{=}C(CO_2Me)CH_2$), 45.2 ($H_2C{=}CHCH_2$), 51.9 (CO_2CH_3), 62.1 (C_{quat}), 66.6 ($PhCH_2$), 118.1 ($H_2C{=}CH$), 124.5 ($H_2C{=}C(CO_2Me)CH_2$), 127.7 (CH_{ar}, *ortho*, *para*), 128.3 (CH_{ar}, *meta*), 134.0 ($H_2C{=}CHCH_2$), 136.9 (C_{ar}), 138.6 ($H_2C{=}C(CO_2Me)CH_2$), 155.9 (CO_2Bn), 166.6 (CO_2Me); HRMS (EI): calcd for $C_{22}H_{29}NO_4Na$ $[M+Na]^+$ 394.19888, found 394.19881.

4.12. Methyl 2-{[[(methyloxy)carbonyl](1-prop-2-en-1-ylcyclohexyl)amino]methyl}prop-2-enoate (16b)

Prepared according to GP2, yield 2.4 g (80%), colorless oil; R_f (Et_2O/toluene, 1:3): 0.71; ^1H NMR (400 MHz, $CDCl_3$): δ=1.05–1.60 (m, 8H, CH_2), 2.17–2.28 (m, 2H, CH_2), 2.65 (d, J=7.3 Hz, 2H, $H_2C{=}CHCH_2$), 3.55 (s, 3H, NCO_2CH_3), 3.70 (s, 3H, CO_2CH_3), 4.06 (s, 2H, $H_2C{=}C(CO_2Me)CH_2$), 4.93–5.03 (m, 2H, $H_2C{=}CH$), 5.60 (s, 1H ($H_2C{=}C(CO_2Me)$, *E*)), 5.66 (ddt, J=17.0, 10.0, 7.3 Hz, 1H, $H_2C{=}CHCH_2$), 6.22 (s, 1H ($H_2C{=}C(CO_2Me)$, *Z*)); ^{13}C NMR (100 MHz, $CDCl_3$): δ=21.5 (CH_2), 22.6 (CH_2), 34.1 ($C_{quat}CH_2$), 36.7 ($H_2C{=}C(CO_2Me)CH_2$), 42.5 ($H_2C{=}CHCH_2$), 51.8 ($H_2C{=}C(CO_2CH_3)$), 52.0 (NCO_2CH_3), 61.8 (C_{quat}), 118.0 ($H_2C{=}CH$), 124.2 ($H_2C{=}C(CO_2Me)$-CH_2), 134.1 ($H_2C{=}CHCH_2$), 138.6 ($H_2C{=}C(CO_2Me)$-CH_2), 156.7 ($HNCO_2CH_3$), 166.6 (CO_2Me); HRMS (EI): calcd for $C_{16}H_{25}NO_4Na$ $[M+Na]^+$ 318.16758, found 318.16757.

4.13. Ethyl 4-({2-[(benzyloxy)carbonyl]prop-2-en-1-yl}{[(benzyl)oxy]carbonyl}amino)-4-prop-2-en-1-ylpiperidine-1-carboxylate (17a)

Prepared according to GP2, yield 2.5 g (80%), colorless oil; R_f (Et_2O/toluene, 1:1): 0.57; ^1H NMR (400 MHz, $CDCl_3$): δ=1.17 (t, J=7.1 Hz, 3H, CH_3CH_2O), 1.62–1.73 (m, 2H, $C_{quat}CH_2$), 2.21–2.30 (m, 2H, $C_{quat}CH_2$), 2.67 (d, J=7.3 Hz, 2H, $H_2C{=}CHCH_2$), 2.92–3.05 (m, 2H, NCH_2), 3.69 (s, 3H, CO_2CH_3), 3.72–3.85 (m, 2H, NCH_2), 4.04 (q, J=7.1 Hz, CH_3CH_2O), 4.06–4.09 (m, 2H, $H_2C{=}C(CO_2Me)CH_2$), 4.91–5.05 (m, 2H, $H_2C{=}CHCH_2$), 5.01 (s, 2H, $PhCH_2$), 5.54 (s, 1H ($H_2C{=}C(CO_2Me)$, *E*)), 5.63 (ddt, J=17.0, 10.0, 7.6 Hz, 1H, $H_2C{=}CHCH_2$), 6.21 (s, 1H ($H_2C{=}C(CO_2Me)$, *Z*), 7.18–7.30 (m, 5H, CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.6 (CH_3CH_2O), 33.5 ($C_{quat}CH_2$), 36.0 ($H_2C{=}C(CO_2Me)CH_2$), 40.2 (NCH_2), 45.4 ($H_2C{=}CHCH_2$), 51.9 (CO_2CH_3), 60.3 (C_{quat}), 61.3 (CH_3CH_2O), 66.8 ($PhCH_2$), 119.2 ($H_2C{=}CHCH_2$), 124.7 ($H_2C{=}C(CO_2Me)$), 127.8 (CH_{ar}, *ortho*), 127.9 (CH_{ar}, *para*), 128.4 (CH_{ar}, *meta*), 132.8 ($H_2C{=}CHCH_2$), 136.5 (C_{ar}), 138.1 ($H_2C{=}C(CO_2Me)CH_2$), 155.3 (CO_2Et), 158.8 (CO_2Bn), 166.3 ($H_2C{=}C(CO_2Me)$); HRMS (EI): calcd for $C_{24}H_{32}N_2O_6Na$ $[M+Na]^+$ 467.21526, found 467.21537.

4.14. Benzyl 4-([(methyloxy)carbonyl]{2-[(methyloxy)-carbonyl]prop-2-en-1-yl}amino)-4-prop-2-en-1-ylpiperidine-1-carboxylate (17b)

Prepared according to GP2, yield 2.1 g (65%), colorless oil; R_f (Et_2O/toluene, 1:3): 0.52; ^1H NMR (400 MHz, $CDCl_3$): δ=1.68–1.80 (m, 2H, $C_{quat}CH_2$), 1.26–2.36 (m, 2H, $C_{quat}CH_2$), 2.73 (d, J=7.6 Hz, 2H, $H_2C{=}CHCH_2$), 2.99–3.15 (m, 2H, NCH_2), 3.61 (s, 3H, $H_2C{=}C(CO_2CH_3)$), 3.75 (NCO_2CH_3), 3.81–3.95 (m, 2H, NCH_2), 4.06–4.10 (m, 2H, $H_2C{=}C(CO_2Me)CH_2$), 5.03–5.15 (m, 2H,

H_2C=$CHCH_2$), 5.09 (s, 2H, $PhCH_2$), 5.59 (s, 1H (H_2C=$C(CO_2Me)$, *E*)), 5.70 (ddt, *J*=17.0, 10.0, 7.6 Hz, 1H, H_2C=$CHCH_2$), 6.27 (s, 1H (H_2C=$C(CO_2Me)$, *Z*)), 7.27–7.37 (m, 5H, CH_{ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ=33.5 ($C_{quat}CH_2$), 36.0 (H_2C=$C(CO_2Me)CH_2$), 40.3 (NCH_2), 45.5 (H_2C=$CHCH_2$), 51.9 (H_2C=$C(CO_2CH_3)$), 52.3 (NCO_2CH3), 60.0 (C_{quat}), 67.1 ($PhCH_2$), 119.1 (H_2C=$CHCH_2$), 124.5 (H_2C=$C(CO_2Me)CH_2$), 127.8 (CH_{ar}, *ortho*), 128.0 (CH_{ar}, *para*), 128.4 (CH_{ar}, *meta*), 132.9 (H_2C=$CHCH_2$), 136.6 (C_{quat}), 138.1 (H_2C=$C(CO_2Me)$), 155.1 (CO_2Bn), 155.6 (NCO_2Me), 166.3 (H_2C=$C(CO_2Me)$); HRMS (EI): calcd for $C_{23}H_{31}N_2O_6$ $[M+H]^+$ 431.21766, found 431.21785.

4.15. 3-Methyl 1-(benzyl)-1-azaspiro[5.5]undec-3-ene-1,3-dicarboxylate (18a)

Prepared according to GP3, yield 460 mg (90%); R_f (Et_2O/toluene, 1:3): 0.79; ^1H NMR (400 MHz, $CDCl_3$): δ=1.23–1.64 (m, 8H, CH_2), 2.28–2.33 (m, 2H, CH_2), 2.35–2.43 (m, 2H, CH_2HC=$C(CO_2Me)$), 3.73 (s, 3H, CO_2CH_3), 4.30 (s, 2H, CH_2N), 5.08 (s, 2H, $PhCH_2$), 6.93–6.98 (m, 1H, CH=$C(CO_2Me)$), 7.27–7.37 (m, 5H, CH_{ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ=22.2 (CH_2), 25.9 (CH_2), 35.2 ($C_{quat}CH_2$), 36.3 (CH_2HC=$C(CO_2Me)$), 42.4 (CH_2N), 51.7 (CO_2CH_3), 56.7 (C_{quat}), 66.8 ($PhCH_2$), 127.7 (CH_{ar}, *ortho*), 127.8 (CH_{ar}, *para*), 128.4 (CH_{ar}, *meta*), 128.9 (HC=$C(CO_2Me)$), 136.8 (C_{ar}), 138.0 (CH=$C(CO_2Me)$), 155.8 (NCO_2Bn), 165.7 (CO_2Me); HRMS (EI): calcd for $C_{20}H_{25}NO_4Na$ $[M+Na]^+$ 366.16758, found 417.16805.

4.16. Dimethyl 1-azaspiro[5.5]undec-3-ene-1,3-dicarboxylate (18b)

Prepared according to GP3, yield 514 mg (94%); R_f (Et_2O/toluene, 1:3): 0.51; ^1H NMR (400 MHz, $CDCl_3$): δ=1.15–1.56 (m, 8H, CH_2), 2.20–2.25 (m, 2H, CH_2), 2.43 (d, *J*=13.1 Hz, 2H, $C_{quat}CH_2HC$=$C(CO_2Me)$), 3.57 (s, 3H, CH=$C(CO_2CH_3)$), 3.68 (s, 3H, NCO_2CH_3), 4.17–4.21 (m, 2H, CH_2N), 6.87–6.92 (m, 1H, CH=$C(CO_2Me)$); ^{13}C NMR (100 MHz, $CDCl_3$): δ=22.2 (CH_2), 25.9 (CH_2), 35.2 ($C_{quat}CH_2$), 36.3 (CH_2HC=), 42.3 (CH_2N), 51.6 (CH=$C(CO_2CH_3)$), 52.2 (NCO_2CH_3), 56.5 (C_{quat}), 128.9 (HC=$C(CO_2Me)$), 138.0 (CH=$C(CO_2Me)$), 156.4 ($HNCO_2CH_3$), 165.7 (H_2C=$C(CO_2Me)$); HRMS (EI): calcd for $C_{14}H_{21}NO_4Na$ $[M+Na]^+$ 290.13628, found 290.13655.

4.17. 9-Ethyl 3-methyl-1-(benzyl)-1,9-diazaspiro[5.5]undec-3-ene-1,3,9-tricarboxylate (19a)

Prepared according to GP3, yield 680 mg (85%); R_f (Et_2O/toluene, 1:3): 0.36; ^1H NMR (400 MHz, $CDCl_3$): δ=1.23 (t, *J*=7.1 Hz, 3H, CH_3CH_2O), 1.38–1.48 (m, 2H, 7-H, 11-H), 2.28–2.35 (m, 2H, 5-H), 2.46–2.65 (m, 2H, 7-H, 11-H), 3.05–3.20 (m, 2H, 8-H, 10-H), 3.70–3.90 (m, 2H, 8-H, 10-H), 3.73 (s, 3H, CO_2CH_3), 4.10 (q, *J*=7.1 Hz, 2H, CH_3CH_2O), 4.21–4.39 (m, 2H, 5-H), 5.07 (s, 2H, $PhCH_2$), 6.94–6.99 (m, 1H, CH=$C(CO_2Me)$), 7.27–7.40 (m, 5H, CH_{ar}); ^{13}C NMR (100 MHz, $CDCl_3$) δ=14.7 (CH_3CH_2O), 34.4 (C-7, C-11), 35.7 (C-5), 40.0 (C-8, C-10), 42.6 (C-2), 51.8 (CO_2CH_3), 54.8 (C-6), 61.2 (CH_3CH_2O), 67.1 ($PhCH_2$), 127.8 (CH_{ar}, *ortho*), 128.0 (CH_{ar}, *para*), 128.5 (CH_{ar}, *meta*), 128.6 (C-3), 136.3 (C_{ar}), 137.2 (C-4), 155.6 (NCO_2Et), 155.9 (NCO_2Bn), 165.4 (CO_2Me); HRMS (EI): calcd for $C_{22}H_{29}N_2O_6$ $[M+H]^+$ 417.20201, found 417.20184.

4.18. 1,3-Dimethyl 9-(benzyl)-1,9-diazaspiro[5.5]undec-3-ene-1,3,9-tricarboxylate (19b)

Prepared according to GP3, yield 1.533 g (90%); R_f (Et_2O/toluene, 1:1): 0.50; ^1H NMR (400 MHz, $CDCl_3$): δ=1.38–1.48 (m, 2H, 7-H, 11-H), 2.25–2.36 (m, 2H, 5-H), 2.45–2.70 (m, 2H, 7-H, 11-H), 3.05–3.25 (m, 2H, 8-H, 10-H), 3.62 (s, 3H, CO_2CH_3), 3.74 (NCO_2CH_3), 3.81–3.95 (m, 2H, 8-H, 10-H), 4.08–4.40 (m, 2H, 2-H), 5.11 (s, 2H, $PhCH_2$), 6.92–6.99 (m, 1H, 4-H), 7.27–7.40 (m, 5H, CH_{ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ=34.4 (C-7, C-11), 35.7 (C-5), 40.1 (C-8, C-10), 42.4 (C-2), 51.7 (CO_2CH_3), 52.4 (NCO_2CH_3), 54.5 (C-6), 66.9 ($PhCH_2$), 128.9 (C-3), 127.7 (CH_{ar}, *ortho*), 127.9 (CH_{ar}, *para*), 128.4 (CH_{ar}, *meta*), 136.7 (C_{ar}), 137.1 (C-4), 155.2 (NCO_2Bn), 156.5 (NCO_2Me), 165.4 (CO_2Me); HRMS (EI): calcd for $C_{21}H_{26}N_2O_6Na$ $[M+Na]^+$ 425.16831, found 425.16836.

4.19. 1-(Benzyl)-1-azaspiro[5.5]undecan-3-one (20)

Prepared according to GP8, yield 79 mg (70%), red crystals, mp 65–67 °C; R_f (Et_2O/toluene, 1:1): 0.76; ^1H NMR (400 MHz, $CDCl_3$): δ=1.23–1.44 (m, 3H, CH_2), 1.46–1.58 (m, 3H, CH_2), 1.63–1.78 (m, 4H, CH_2), 1.88 (t, *J*=6.7 Hz, 2H, 5-H), 2.36 (t, *J*=6.7 Hz, 2H, 4-H), 3.02 (s, 2H, 2-H), 3.60 (s, 2H, $PhCH_2$), 7.10–7.30 (m, 5H, CH_{ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ=22.1 (C-8,10), 26.1 (C-9), 30.8 (C-5), 32.3 (C-7,11), 35.6 (C-4), 51.5 ($PhCH_2$), 54.6 (C-6), 55.5 (C-2), 126.8 (CH_{ar}, *para*), 128.3 (CH_{ar}, *ortho*, *meta*), 140.0 (C_{ar}), 212.0 (C=O); HRMS (EI): calcd for $C_{17}H_{24}NO$ $[M+H]^+$ 258.18524, found 258.18503.

4.20. Ethyl 3-oxo-1-(benzyl)-1,9-diazaspiro[5.5]undecane-9-carboxylate (21)

Prepared according to GP8, yield 80 mg (65%), red crystals, mp 95–97 °C; R_f (Et_2O/toluene, 1:1): 0.43; ^1H NMR (400 MHz, $CDCl_3$): δ=1.20 (t, *J*=7.1 Hz, 3H, CH_3CH_2O), 1.47–1.66 (m, 2H, 7,11-H), 1.88–2.05 (m, 4H, 7,11-H, 5-H), 2.37–2.48 (m, 2H, 4-H), 3.06 (s, 2H, 2-H), 3.24–3.40 (m, 2H, 8,10-H), 3.61 (s, 2H, $PhCH_2$), 3.67–3.82 (m, 2H, 8,10-H), 4.08 (q, *J*=7.1 Hz, 2H, CH_3CH_2O), 7.10–7.30 (m, 5H, CH_{ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.7 (CH_3CH_2O), 30.5 (C-5), 32.1 (C-7,11), 35.5 (C-4), 39.8 (C-8,10), 51.5 (C-2), 53.4 (C-6), 55.3 ($PhCH_2$), 61.4 (CH_3CH_2O), 127.1 (CH_{ar}, *para*), 128.2 (CH_{ar}, *ortho*), 128.4 (CH_{ar}, *meta*), 139.0 (C_{ar}), 155.6 (NCO_2Et), 211.0 (C=O); HRMS (EI): calcd for $C_{19}H_{27}N_2O_3$ $[M+H]^+$ 331.20162, found 331.20159.

4.21. Benzyl 3-oxo-1-azaspiro[5.5]undecane-1-carboxylate (22a)

Prepared according to GP8, yield 240 mg (66%), white crystals, mp 85–87 °C; R_f (Et_2O/toluene, 1:1): 0.78; ^1H NMR (400 MHz, $CDCl_3$): δ=1.10–1.67 (m, 8H, CH_2), 1.96–2.04 (m, 2H, CH_2), 2.31–2.39 (m, 2H, 5-H), 2.61–2.74 (m, 2H, 4-H), 4.08 (s, 2H, 2-H), 5.02 (s, 2H, $PhCH_2$), 7.27–7.37 (m, 5H, CH_{ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ=22.3 (C-8,10), 24.9 (C-9), 28.6 (C-5), 31.3 (C-7,11), 34.3 (C-4),

52.0 (C-2), 58.8 (C-6), 67.0 ($PhCH_2$), 127.9 (CH_{ar}, *ortho*), 128.0 (CH_{ar}, *para*), 128.5 (CH_{ar}, *meta*), 136.3 (C_{ar}), 154.7 (NCO_2Bn), 208.3 (C=O); HRMS (EI): calcd for $C_{18}H_{23}NO_3Na$ $[M+Na]^+$ 324.15701, found 324.15695.

4.22. Methyl 3-oxo-1-azaspiro[5.5]undecane-1-carboxylate (22b)

Prepared according to GP8, yield 184 mg (60%), colorless oil; R_f (Et_2O/toluene, 1:1): 0.47; ^1H NMR (400 MHz, $CDCl_3$): δ=1.19–1.67 (m, 8H, CH_2), 1.96–2.03 (m, 2H, CH_2), 2.31–2.39 (m, 2H, 5-H), 2.59–2.69 (m, 2H, 4-H), 3.57 (s, 3H, $COOCH_3$), 4.04 (s, 2H, 2-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=23.0 (C-8,10), 24.9 (C-9), 28.5 (C-5), 31.2 (C-7,11), 34.2 (C-4), 51.9 (C-2), 52.1 ($COOCH_3$), 58.6 (C-6), 155.3 (NCO_2Me), 208.3 (C=O); HRMS (EI): calcd for $C_{12}H_{20}NO_3$ $[M+H]^+$ 226.14377, found 226.14600.

4.23. 9-Ethyl 1-(benzyl)-3-oxo-1,9-diazaspiro[5.5]undecane-1,9-dicarboxylate (23a)

Prepared according to GP8, yield 340 mg (70%), colorless oil; R_f (Et_2O/toluene, 1:1): 0.24; ^1H NMR (400 MHz, $CDCl_3$): δ=1.13–1.26 (m, 3H, CH_3CH_2O), 1.40–1.56 (m, 2H, 7,11-H), 2.00–2.11 (m, 2H, 7,11-H), 2.34–2.47 (m, 2H, 5-H), 2.77–3.05 (m, 4H, 4-H, 8,10-H), 3.85–4.20 (m, 6H, 8,10-H, 2-H, CH_3CH_2O), 5.02 (s, 2H, $PhCH_2$), 7.15–7.40 (m, 5H, CH_{ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.6 (CH_3CH_2O), 28.6 (C-5), 31.1 (C-7,11), 34.0 (C-4), 40.5 (C-8,10), 52.0 (C-2), 56.9 (C-6), 61.4 (CH_3CH_2O), 67.3 ($PhCH_2$), 128.0 (CH_{ar}, *ortho*), 128.2 (CH_{ar}, *para*), 128.5 (CH_{ar}, *meta*), 135.9 (C_{ar}), 154.6 (NCO_2Bn), 155.3 (NCO_2Et), 207.1 (C=O).

4.24. 1-Methyl 9-(benzyl)-3-oxo-1,9-diazaspiro[5.5]undecane-1,9-dicarboxylate (23b)

Prepared according to GP8, yield 800 mg (63%), white crystals, mp 108–111 °C; R_f (Et_2O/toluene, 1:1): 0.36; ^1H NMR (400 MHz, $CDCl_3$): δ=1.40–1.56 (m, 2H, 7,11-H), 2.01–2.07 (m, 2H, 7,11-H), 2.36–2.42 (m, 2H, 5-H), 2.78–2.90 (m, 2H, 4-H), 2.92–3.07 (m, 2H, 8,10-H), 3.59 (CO_2CH_3), 3.90–4.10 (m, 2H, 8,10-H), 4.06 (s, 2H, 2-H), 5.02–5.12 (m, 2H, $PhCH_2$), 7.21–7.31 (m, 5H, CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ=28.7 (C-5), 31.1 (C-7,11), 33.9 (C-4), 40.7 (C-8,10), 51.9 (C-2), 52.5 (CO_2CH_3), 56.6 (C-6), 67.1 ($PhCH_2$), 127.8 (CH_{ar}, *ortho*), 127.9 (CH_{ar}, *para*), 128.4 (CH_{ar}, *meta*), 136.7 (C_{ar}), 155.1 (NCO_2Bn), 155.3 (NCO_2Me), 207.1 (C=O); HRMS (EI): calcd for $C_{19}H_{24}N_2O_5Na$ $[M+Na]^+$ 383.15774, found 383.15760.

4.25. Benzyl {1-[(4-methylphenyl)sulfonyl]-3-prop-2-en-1-ylpiperidin-3-yl}carbamate (25)

Prepared according to GP3, yield 1.07 g (25%), colorless oil; R_f (Et_2O/toluene, 2:1): 0.75; ^1H NMR (400 MHz, $CDCl_3$): δ=1.05–1.20 (m, 1H, CH_2), 1.55–1.67 (m, 1H, CH_2), 1.71–1.86 (m, 1H, CH_2), 2.17–2.53 (m, 7H, CH_2, H_2C=CHCH_2, CH_3), 4.93–5.17 (m, 5H, $PhCH_2$, H_2C=, NH), 5.64–5.76 (m, 1H, H_2C=C$H$$CH_2$), 7.27–7.39 (m, 7H, CH_{ar}), 7.57–7.64 (m, 2H, CH_{ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ=20.9 (CH_2CH_2N), 21.5 (CH_3), 31.0 (C-4), 39.4 (CH_2NCH_2), 40.2 (H_2C=CHCH_2), 46.4 (CH_2CH_2N), 53.2 (C_{quat}), 53.8 ($C_{quat}CH_2N$), 66.3 ($PhCH_2$), 119.2 (H_2C=CH), 127.5 (CH_{ar}, *ortho*, Ts), 128.0 (CH_{ar}, *ortho*, Bn), 128.1 (CH_{ar}, *para*, Bn), 128.5 (CH_{ar}, *meta*, Bn), 129.8 (CH_{ar}, *meta*, Ts), 132.2 (H_2C=$CH$$CH_2$), 133.0 ($O_2SC$, Ts), 136.5 ($C_{ar}$, Bn), 143.7 ($CH_3C_{ar}$, Ts), 154.5 ($CO_2Bn$).

4.26. Methyl 2-[([(benzyloxy)carbonyl]{1-[(4-methylphenyl)sulfonyl]-3-prop-2-en-1-ylpiperidin-3-yl}amino)methyl]prop-2-enoate (26)

Prepared according to GP2, yield 600 mg (50%), colorless oil; R_f (Et_2O/toluene, 2:1): 0.71; ^1H NMR (400 MHz, $CDCl_3$): δ=1.50–1.87 (m, 4H, CH_2), 2.35 (s, 3H, CH_3), 2.45–2.58 (m, 2H, CH_2), 2.73–2.92 (m, 2H, CH_2), 3.27–3.45 (m, 1H, CH_2), 3.70 (d, J=11.1 Hz, 1H, CH_2), 3.67 (s, 3H, CO_2CH_3), 3.73–3.84 (m, 1H, CH_2), 3.99–4.08 (m, 2H, CH_2), 4.16–4.24 (m, 2H, CH_2), 4.90–5.13 (m, 4H, H_2C=CHCH_2, $PhCH_2$), 5.53 (s, 1H (H_2C=C(COOMe), *E*)), 5.61 (m, 1H, H_2C=C$H$$CH_2$), 6.17 (s, 1H ($H_2C$=C(COOMe), *Z*)), 7.18–7.33 (m, 7H, CH_{ar}), 7.48–7.54 (m, 2H, CH_{ar}, *ortho*, Ts,); ^{13}C NMR (100 MHz, $CDCl_3$): δ=21.4 (CH_2), 21.5 (CH_3), 31.3 ($C_{quat}CH_2$), 37.0 (H_2C=C(CO_2Me)CH_2), 45.3 (H_2C=CHCH_2), 46.0 (CH_2NTs), 49.7 (CO_2CH_3), 52.8 ($ZNCH_2C(CO_2Me)$), 60.5 (C_{quat}), 67.1 ($PhCH_2$), 68.8 ($C_{quat}CH_2NTs$), 119.3 (H_2C=$CHCH_2$), 124.9 (H_2C=C(CO_2Me)), 127.5 (CH_{ar}, *ortho*, Ts, CH_{ar}, *para*, Bn), 128.0 (CH_{ar}, *ortho*, Bn), 128.4 (CH_{ar}, *meta*, Bn), 129.7 (CH_{ar}, *meta*, Ts), 129.8 (CH_2CH=$C(CO_2Me)$), 132.6 (H_2C=$CHCH_2$), 133.4 (O_2SC_{ar}, Ts), 136.4 (C_{ar}, Bn), 138.0 (H_2C=$C(CO_2Me)$), 143.4 (CH_3C_{ar}, Ts), 155.9 (CO_2Bn), 166.4 (CO_2CH_3).

4.27. 1-Benzyl 3-methyl 8-[(4-methylphenyl)sulfonyl]-1,8-diazaspiro[5.5]undec-3-ene-1,3-dicarboxylate (27)

Prepared according to GP7, yield 370 mg (65%), white crystals, mp 133–135 °C; R_f (Et_2O/toluene, 1:1): 0.55; ^1H NMR (400 MHz, $CDCl_3$): δ=1.40–1.80 (m, 3H, CH_2), 2.25–2.75 (m, 4H, CH_2), 2.35 (s, 3H, $ArCH_3$), 2.96–3.06 (m, 1H, CH_2), 3.12–3.24 (m, 1H, CH_2), 3.27–3.45 (m, 1H, CH_2), 3.70 (d, J=11.1 Hz, 1H, CH_2), 3.70 (s, 3H, CO_2CH_3), 4.20–4.43 (m, 2H, 7-H), 5.00 (s, 2H, $PhCH_2$), 6.93–7.02 (m, 1H, 3-H), 7.15–7.35 (m, 7H, CH_{ar}), 7.45–7.60 (m, 2H, CH_{ar}, *ortho*, Ts); ^{13}C NMR (100 MHz, $CDCl_3$): δ=21.5 (CH_3), 21.9 (C-10), 31.9 (C-11), 32.8 (C-5), 41.9 (C-2), 46.8 (C-9), 51.9 (CO_2CH_3), 52.2 (C-7), 56.1 (C-6), 67.0 ($PhCH_2$), 127.5 (CH_{ar}, *ortho*, Ts), 127.7 (CH_{ar}, *ortho*, Bn), 128.0 (CH_{ar}, *para*, Bn), 128.5 (CH_{ar}, *meta*, Bn), 129.7 (CH_{ar}, *meta*, Ts), 129.8 (C-3), 133.4 (O_2SC_{ar}, Ts), 136.4 (C_{ar}, Bn), 137.2 (C-4), 143.5 (CH_3C_{ar}, Ts), 155.1 (NCO_2Bn) 165.2 (CO_2CH_3); HRMS (EI): calcd for $C_{26}H_{31}N_2O_6S$ $[M+H]^+$ 499.18973, found 499.18978.

4.28. Methyl 8-[(4-methylphenyl)sulfonyl]-3-oxo-1,8-diazaspiro[5.5]undecane-1-carboxylate (28)

Prepared according to GP8, yield 170 mg (50%), white crystals, mp 89–91 °C; R_f (Et_2O/toluene, 1:1): 0.33; ^1H NMR (400 MHz, $CDCl_3$): δ=1.50–1.90 (m, 4H, H-10,11), 2.15–2.26 (m, 1H, CH_2), 2.31–2.41 (m, 4H, CH_3, CH_2), 2.42–2.66 (m, 3H, CH_2), 3.49 (dd, J=11.5, 16.8 Hz, 2H, 2-H), 3.70 (d, J=11.1 Hz, 1H, CH_2), 3.89 (d, J=18.4 Hz, 1H, 7-H), 4.24 (d, J=18.4 Hz, 1H, 7-H), 4.94 (dd, J=12.3,

19.6 Hz, 2H, $PhCH_2$), 7.14–7.29 (m, 7H, CH_{ar}), 7.53 (m, 2H, CH_{ar}, *ortho*, Ts); ^{13}C NMR (100 MHz, $CDCl_3$): δ=21.5 (CH_3), 22.2 (C-10), 27.2 (C-5), 29.5 (C-11), 33.8 (C-4), 45.8 (C-9), 48.5 (C-7), 52.0 (C-2), 57.3 (C-6), 66.4 ($PhCH_2$), 127.2 (CH_{ar}, *ortho*, Ts), 127.9 (CH_{ar}, *ortho*, Bn), 128.2 (CH_{ar}, *para*, Bn), 128.5 (CH_{ar}, *meta*, Bn), 129.7 (CH_{ar}, *meta*, Ts), 133.7 (O_2SC_{ar}), 135.6 (C_{ar}, Bn), 143.5 (CH_3C_{ar}, Ts), 154.5 (NCO_2Bn), 206.4 (C=O); HRMS (EI): calcd for $C_{24}H_{28}N_2O_5SNa$ $[M+Na]^+$ 479.16111, found 479.16142.

4.29. Dimethyl 1-azaspiro[5.5]undecane-1,3-dicarboxylate (29)

To a solution of the unsaturated ester **18b** (180 mg, 0.67 mmol) in dry MeOH (10 mL), Mg turnings (65 mg, 2.7 mmol, 4 equiv) were added, and the reaction mixture was vigorously stirred for 7 h. Thereafter, the resulting gel was partitioned between saturated NH_4Cl solution (25 mL) and Et_2O (25 mL). The aqueous phase was extracted with Et_2O (3×10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and evaporated to give 180 mg (100%) of ester **29** as a colorless oil, pure enough for the next transformation. ^1H NMR (400 MHz, $CDCl_3$): δ=1.23–1.58 (m, 8H, CH_2), 1.64–1.69 (m, 2H, CH_2), 1.72–1.89 (m, 2H, CH_2), 2.30–2.40 (m, 1H, $CHCO_2Me$), 2.51–2.69 (m, 2H, CH_2), 3.35 (dd, *J*=14.0, 9.7 Hz, 1H, 2-H), 3.56 (s, 3H, $CH(CO_2CH_3)$), 3.61 (s, 3H, NCO_2CH_3), 3.93 (dd, *J*=14.0, 5.1 Hz, 1H, 2-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=20.1 (C-4), 22.2 (C-9), 22.7, 25.2 (C-8,10), 30.0 (C-5), 31.9, 33.1 (C-7,11), 39.6 ($HC(CO_2CH_3)$), 41.5 (CH_2N), 51.5 ($HC(CO_2CH_3)$), 51.7 (NCO_2CH_3), 58.5 (C_{quat}), 155.8 (NCO_2Me), 174.2 ($HC(CO_2Me)$); HRMS (EI): calcd for $C_{14}H_{23}NO_4Na$ $[M+Na]^+$ 292.15193, found 292.15197.

4.30. 1-[(Methyloxy)carbonyl]-1-azaspiro[5.5]-undecane-3-carboxylic acid (30)

A solution of ester **29** (160 mg, 0.6 mmol) in a mixture of THF (3 mL), MeOH (2 mL), and H_2O (1 mL) was treated with LiOH (200 mg, 5.0 mmol, 8 equiv) and stirred for 3 h at room temperature. The completion of reaction was confirmed by TLC. The reaction mixture was then concentrated under reduced pressure to remove the bulk of the solvents. The residue was partitioned between saturated NH_4Cl solution (10 mL) and Et_2O (10 mL). The aqueous phase was extracted with Et_2O (2×5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo, yielding acid **30** (150 mg, 100%), which was pure enough for the next transformation. ^1H NMR (400 MHz, $CDCl_3$): δ=1.22–1.59 (m, 8H, CH_2), 1.63–1.72 (m, 2H, CH_2), 1.75–1.90 (m, 2H, CH_2), 2.30–2.40 (m, 1H, CH), 2.51–2.69 (m, 2H, CH_2), 3.34–3.46 (m, 1H, H-2), 3.57 (s, 3H, NCO_2CH_3), 3.86–4.00 (m, 1H, H-2), 8.10–8.80 (br s, 1H, COOH); ^{13}C NMR (100 MHz, $CDCl_3$): δ=20.3 (C-4), 22.4 (C-9), 22.9, 25.2 (C-8,10), 30.0 (C-5), 32.1, 33.2 (C-7,11), 39.9 ($HC(CO_2CH_3)$), 41.6 (CH_2N), 52.0 (NCO_2CH_3), 58.8 (C_{quat}), 156.3 (NCO_2Me).

4.31. Methyl 3-{[(benzyl)amino]carbonyl}-1-azaspiro-[5.5]undecane-1-carboxylate (31)

To a solution of acid **30** (75 mg, 0.3 mmol) in DMF (5 mL) was added CDI (64 mg, 0.4 mmol, 1.3 equiv) followed by stirring the mixture at 50 °C for 2 h. Then, benzylamine (65 mg, 65 μL, 0.6 mmol, 2 equiv) was added and stirring continued for 8 h at 60 °C. After cooling, the mixture was partitioned between 1 N HCl (25 mL) and CH_2Cl_2 (10 mL). The organic layer was separated, washed with saturated aqueous $NaHCO_3$ solution, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (toluene/Et_2O, 2:1) to give amide **31** (80 mg, 78%) as a colorless oil; R_f (Et_2O/toluene, 1:1): 0.40; ^1H NMR (400 MHz, $CDCl_3$): δ=1.08–1.87 (m, 13H, CH, CH_2), 2.29–2.56 (m, 3H, CH, CH_2), 3.42–3.51 (m, 1H, CH_2), 3.47 (s, 3H, $CH(CO_2CH_3)$), 3.61 (s, 3H, NCO_2CH_3), 3.75 (dd, *J*=14.3, 4.9 Hz, 1H, H-2), 4.31 (d, *J*=5.1 Hz, 2H, $PhCH_2N$), 6.49 (s, 1H, C(O)NH), 7.13–7.27 (m, 5H, CH_{ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ=21.2 (C-4), 22.4 (C-9), 22.8, 25.3 (C-8,10), 29.9 (C-5), 31.7, 33.2 (C-7,11), 41.4 ($HCCO_2Me$), 42.1 ($PhCH_2N$), 43.3 (CH_2N), 51.8 (NCO_2CH_3), 58.9 (C_{quat}), 127.3 (CH_{ar}, *para*), 127.6 (CH_{ar}, *ortho*), 128.5 (CH_{ar}, *meta*), 138.2 (C_{ar}), 156.3 (NCO_2CH_3), 173.9 ($C(O)NHBn$)); HRMS (EI): calcd for $C_{20}H_{29}N_2O_3$ $[M+H]^+$ 345.21727, found 345.21701.

4.32. Methyl 3-(1-piperazinylcarbonyl)-1-azaspiro[5.5]undecane-1-carboxylate (32)

To a solution of acid **30** (75 mg, 0.3 mmol) in DMF (5 mL) was added CDI (64 mg, 0.4 mmol, 1.3 equiv) followed by stirring the mixture at 65 °C for 2 h. Then, piperazine (120 mg, 1.5 mmol, 5 equiv) was added and stirring continued for 5 h at 65 °C. After cooling, the mixture was partitioned between 1 N HCl (25 mL) and CH_2Cl_2 (10 mL). The organic layer was separated, washed with saturated aqueous $NaHCO_3$ solution, dried over Na_2SO_4, filtered, and concentrated in vacuo resulting in amide **32** (82 mg, 80%) as a yellow oil; R_f (Et_2O/CH_2Cl_2, 1:1): 0.13; ^1H NMR (400 MHz, $CDCl_3$): δ=1.25–1.93 (m, 12H, CH_2), 2.20–2.49 (m, 2H, CH_2), 2.61–2.92 (m, 6H, CH_2), 3.22–3.32 (m, 1H, CH), 3.35–3.62 (m, 4H, CH_2), 3.57 (s, 3H, $CH(CO_2CH_3)$), 3.86–3.96 (dd, *J*=14.0, 3.8 Hz, 1H, H-2); ^{13}C NMR (100 MHz, $CDCl_3$): δ=20.0 (C-4), 22.0 (C-9), 22.9, 25.3 (C-8,10), 30.4 (C-5), 32.8, 33.1 (C-7,11), 36.9 ($HC(CO_2CH_3)$), 42.1, 42.4 ($CH_2N(CO)CH_2$), 45.6 (CH_2N), 46.3 (CH_2NHCH_2), 51.7 (NCO_2CH_3), 58.7 (C_{quat}), 156.0 (NCO_2Me), 172.0 ($HC(C(O)N)$); HRMS (EI): calcd for $C_{17}H_{30}N_3O_3$ $[M+H]^+$ 324.22817, found 324.22812.

4.33. Benzyl 3-hydroxy-3-phenyl-1-azaspiro[5.5]-undecane-1-carboxylate (33)

To a vigorously stirred solution of ketone **22a** (90 mg, 0.3 mmol) in THF (2 mL) was added a solution of PhMgBr (200 μL, 3 M in Et_2O, 0.6 mmol, 2 equiv) at −40 °C in a dropwise fashion. The reaction mixture was then allowed to reach room temperature within 1 h. The reaction was quenched by the addition of saturated NH_4Cl solution (5 mL) and extracted with Et_2O (2×10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (toluene/Et_2O, 2:1) to give alcohol **34** (70 mg, 60%) as white crystals, mp 125–127 °C; R_f (Et_2O/toluene, 1:3): 0.58; ^1H NMR (400 MHz, $CDCl_3$): δ=1.26–1.62 (m, 10H, $5CH_2$), 1.68–1.77 (m, 1H, CH_2), 1.95–2.14 (m, 2H, CH_2), 2.31–2.41 (m, 1H, CH_2), 2.69–2.79 (m, 1H, CH_2), 3.51 (d,

J=14.5 Hz, 1H, 2-H), 3.87 (d, J=14.5 Hz, 1H, 2-H), 5.02 (s, 2H, $PhCH_2$), 7.13–7.28 (m, 8H, CH_{ar}), 7.39 (d, J=7.3 Hz, 2H, CH_{ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ=22.3, 22.9 (C-8,10), 25.6 (C-9), 29.9 (C-5), 32.1, 33,6 (C-7,11), 34.2 (C-4), 52.2 (C-2), 58.9 (C-6), 66.8 ($PhCH_2$), 72.9 (C-3), 124.5 (CH_{ar}, *ortho*), 127.1 (CH_{ar}, *para*), 127.8 (CH_{ar}, *meta*, *para*), 128.3 (CH_{ar}, *ortho*), 128.4 (CH_{ar}, *meta*), 136.7 (C_{ar}), 146.3 (C_{ar}), 156.6 (NCO_2Bn); HRMS (EI): calcd for $C_{24}H_{30}NO_3$ $[M+H]^+$ 380.22202, found 380.22193.

4.34. 3-Phenyl-1-azaspiro[5.5]undecan-3-ol (34)

A flask containing a solution of benzyl carbamate **33** (7.2 mg, 0.02 mmol) and 10% Pd/C (1 mg) in EtOH (1 mL) was connected to a ballon filled with hydrogen. The suspension was stirred at room temperature for 4 h and then filtered through a pad of Celite. The filtrate was concentrated in vacuo to give amino alcohol **34** (5 mg, 100%) as white crystals, mp 110–112 °C; R_f (Et_2O/toluene, 3:1): 0.2; ^1H NMR (400 MHz, $CDCl_3$): δ=1.25–1.78 (m, 13H, CH*H*, $6CH_2$), 1.92–2.04 (m, 1H, CH_2), 2.63 (d, J=12.5 Hz, 1H, 2-H), 3.10 (d, J=12.5 Hz, 1H, 2-H), 2.70–3.90 (br s, 2H, OH, NH), 7.19 (t, J=7.3 Hz, 1H, CH_{ar}, *para*), 7.28 (t, J=7.3 Hz, 2H, CH_{ar}, *meta*), 7.44 (d, J=7.3 Hz, 2H, CH_{ar}, *ortho*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=21.8, 21.9 (C-8,10), 26.2 (C-9), 29.3 (C-4), 31.3 (C-5), 32.7 (C-7), 40.6 (C-11) 50.7 (C-6), 51.2 (C-2), 70.6 (C-3), 124.7 (CH_{ar}, *ortho*), 126.9 (CH_{ar}, *para*), 128.2 (CH_{ar}, *meta*), 145.9 (C_{ar}); HRMS (EI): calcd for $C_{16}H_{24}NO$ $[M+H]^+$ 246.18524, found 258.18518.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.07.083.

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