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A double alkylation—ring closing metathesis approach to spiroimines

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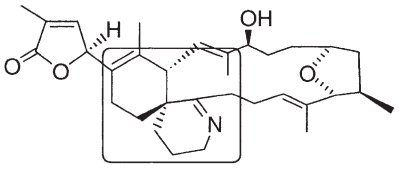
Abstract—As part of a programme directed towards the synthesis of the marine toxins, the spirolides and gymnodimine, a convenient synthesis of the key bicyclic spiroimine ring systems has been developed. The method involves double alkylation of a simple lactam, Grubbs ring closing metathesis of the resultant dialkylated lactam then reduction of the lactam to an imine.

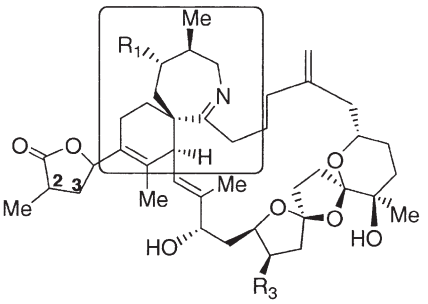
1. Introduction

Several shellfish toxins[1] formed during algal blooms contain spiroimine units as a key structural feature. Gymnodimine[2] (**1**) is a biotoxin isolated from New Zealand oysters (*Tiostrea chilensis*) that exhibits neurotoxic effects in a mouse bioassay and contains an azaspiro[5.5]undecadiene subunit. This 6,6-spirocyclic ring system is also present in the fast acting toxin spirocentrimine[3] isolated from a Taiwanese laboratory-cultured *Procentrum* species.



Gymnodimine **1**

The homologous azaspiro[5.6]dodecadiene ring system is a key structural feature of the macrocyclic toxins, spirolides A–D (**2**-**5**), isolated from the digestive glands of contaminated mussels (*Mytilus edulis*), scallops (*Placopecten magellanicus*) and toxic plankton from the eastern coast of Nova Scotia, Canada. Initially the structures of spirolides B (**3**) and D (**5**) were elucidated[4] together with spirolides E and F[5] that lacked the spiroimine unit. More recently, isolation and culture of a toxic clone of the dinoflagellate *Alexandrium ostenfeldii*, obtained from the same aquaculture site, allowed structural elucidation of spirolides A (**2**) and C (**3**).[6,7] The spirolides activate L-type calcium channels and act as muscarinic acetylcholine receptor antagonists. The key 7,6-spirocyclic imine pharmacophore present in the spirolides is also found in the related shellfish toxins, the pinnatoxins[8,9] and pteriatoxin.[10]



Spirolide A **2**; $\Delta_{2,3}$, R_1=H, R_2=Me
Spirolide B **3**; R_1=H, R_2=Me
Spirolide C **4**; $\Delta_{2,3}$, R_1=Me, R_2=Me
Spirolide D **5**; R_1=Me, R_2=Me

Gymnodamine in which the imine moiety is reduced, resulted in a significant decrease in toxicity[11] and the keto amine hydrolysis products of spirolides A–D, namely spirolides E and F, are also inactive[5] suggesting that the spiroimine portion of these shellfish toxins is the active

Keywords: Gymnodimi; Spirolactams; β-Trimethylsilylethoxycarbonyl (TEOC).
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pharmacophore. The mechanism of action of these imine-containing toxins was initially thought to involve covalent bond formation via nucleophilic addition to the imine, however Romo et al.[12] postulate that these α-quaternary substituted imines may serve as latent nucleophiles as a result of their masked enamine character as evidenced by their ability to completely incorporate deuterium at the exocyclic carbon after prolonged exposure to CD_3OD.

Diels–Alder cycloaddition of dienes to α-methylene lactams has provided an efficient method for the construction of the spirocyclic imine unit in gymnodimine[13,14] and pinnatoxin A.[15] White et al.[16] also recently reported a synthesis of the spiroimine unit of gymnodimine (**1**) via elaboration of a Diels–Alder adduct formed using an α-methylene derivative of Meldrum's acid as the dienophile. Other approaches to the spirocyclic imine unit in pinnatoxin A include the use of an aza-Wittig reaction of an azidoketone[17] and thermolysis of an aminoketone.[18] Prompted by the interesting architecture and biological activity of these spirocyclic imines present in these highly toxic shellfish toxins, we directed our attention to the synthesis of a range of spirocyclic imines as potential pharmacological probes. We therefore, herein report the full details[19] of an efficient synthesis of spirocyclic imines from simple lactams via double alkylation to generate a diene precursor followed by Grubbs' ring closing metathesis and reduction of the lactam to an imine (Scheme 1).

2. Results and discussion

Our initial attention focused on the synthesis of the parent spiroimine ring systems present in gymnodimine (**1**) and the spirolides (**2**-**5**) with the idea that nucleophilic addition of an organometallic species to the imine carbon[20] followed by reformation of the imine[21] from the resultant substituted amine would provide the methodology to access the substituted imine units present in the natural products. Our work was prompted by the use of an analogous double alkylation—ring closing metathesis strategy to construct bicyclic lactam peptidomimetics[22] and enantiopure spirocycles.[23]

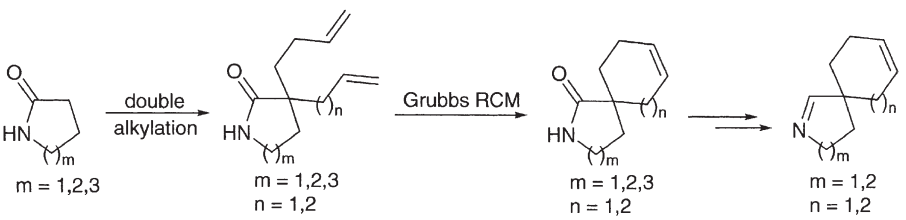
Initial attention focused on the lactam double α-alkylation step that required considerable experimentation to ascertain the optimum procedure. In analogous alkylation steps, lactams are often protected as *tert*-butoxycarbamates[22] or *N*-benzyl derivatives.[24,25] These bulky groups hindered the second alkylation step and base induced ring opening proved problematic when using a seven membered acylated lactam. In search of a general method for effecting an efficient double alkylation procedure we focused on the use of *N*-trimethylsilyl lactam derivatives. Covey et al.[26] have used *N*-trimethylsilyl lactams for the synthesis of α,α-dialkyl-ε-caprolactams however in their case the *N*-trimethylsilyl lactams were prepared in a separate step in benzene using triethylamine and trimethylsilyl chloride.

In the present work the *N*-trimethylsilyl lactams were prepared by treatment of the parent lactam with butyllithium in THF at −78 °C followed by quenching with trimethylsilyl chloride. The first α-alkylation step was then carried out directly without isolation and purification of the *N*-trimethylsilyl lactam. Five, six and seven membered lactams were doubly alkylated following similar conditions to that reported by Meyers et al.[27,28] (LDA, THF, −78 °C) thus providing the dialkylated dienes (**6**-**11**) listed in Table 1. In the case of the unsymmetrically disubstituted dienes (**6**), (**8**) and (**10**) the alkylation steps were performed sequentially whereas in the case of the symmetrically substituted dienes (**7**), (**9**), and (**11**) the double alkylation was effected in one step using two equivalents of base with excess electrophile. Given that lower yields were observed for the second alkylation step in the case of the unsymmetrical dienes (**6**), (**8**), and (**10**), the initial first alkylation was always carried out with the less reactive halide and the more reactive allyl halides were used in the second alkylation step.

With the dienes (**6**-**11**) in hand, ring closing metathesis[29–34] proceeded smoothly in excellent yield using 5% Grubbs catalyst $[Cl_2(PCy_3)_2RuCHPh]$ at room temperature affording spirolactams (**12**-**17**) with various appended ring sizes.

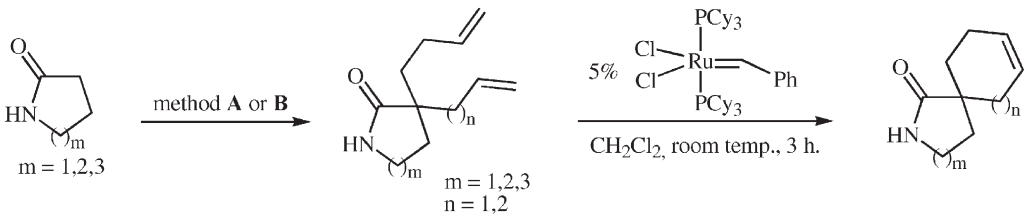
Our efforts next focused on the subsequent conversion of the spirolactams to spiroimines (Table 2).[35–37] After much experimentation, it was found that the optimum procedure involved protection of the five and six membered lactams (**12**-**15**) as the fluoride-labile β-trimethylsilylethoxycarbonyl (TEOC) group[38] followed by reduction of the amide carbonyl group using lithium triethylborohydride[39] as described by Grieco and Kaufman.[40] The TEOC group was introduced employing butyllithium and 2-(trimethylsilyl)ethyl 4-nitrophenyl carbonate providing the TEOC protected lactams (**18**-**21**). Subsequent reduction with lithium triethylborohydride at −78 °C followed by immediate exposure to tetrabutylammonium fluoride afforded the spirocyclic imines (**22**-**25**) in good yield. Spiroimines (**22**-**25**) were readily purified by flash chromatography and did not undergo decomposition upon prolonged storage at room temperature.

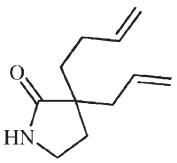
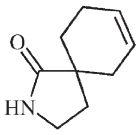
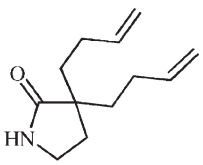
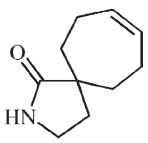
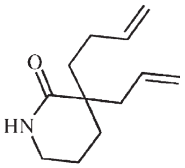
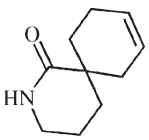
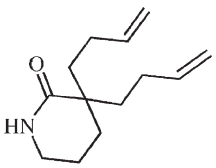
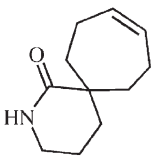
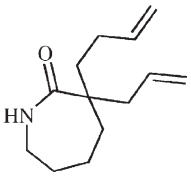
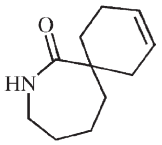
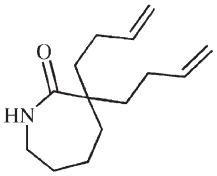
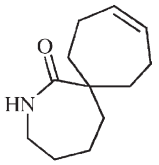
This reduction procedure proved a reliable method for the preparation of spirolactams containing a five or six membered lactam ring, however, in the case of TEOC protected spirolactam (**26**) in which the lactam was



Scheme 1.

Table 1. Preparation of spirolactams



Entry	Dialkylated lactam (yield %, method[a,b])	Spirolactam (yield %)
1	 **6** 74%, A	 **12**, 86%
2	 **7** 71%, B	 **13**, 93%
3	 **8** 81%, A	 **14**, 90%
4	 **9** 78%, B	 **15**, 95%
5	 **10** 67%, A	 **16**, 88%
6	 **11** 77%, B	 **17**, 92%

[a] Method A: (i) *n*-BuLi (1.05 equiv.), THF, −78 °C, $SiMe_3Cl$ (1.05 equiv.) −78 °C to 0 °C; (ii) LDA (1 equiv.), THF, −78 °C, 4-bromo-1-butene (1.05 equiv.) −78 °C to 0 °C; (iii) LDA (1.1 equiv.) −78 °C, allyl iodide (1.25 equiv.), −78 °C to 0 °C.

[b] Method B: (i) *n*-BuLi (1.05 equiv.), −78 °C, $SiMe_3Cl$ (1.05 equiv.), −78 °C to 0 °C; (ii) LDA (2.3 equiv.) −78 °C, 4-bromo-1-butene (2.5 equiv.), −78 °C to 0 °C.

embedded in a seven membered ring an alternative mode of reduction took place. In this case reduction of the carbamate carbonyl group took place in preference to the lactam carbonyl group resulting in formation of *N*-formyl spirolactam (**27**) (Scheme 2). This result is readily rationalized by examination of the minimum energy conformation of the 6,6-spirolactam (**20**) compared to the 7,6-spirolactam (**26**) (Fig. 1). Simple molecular models and semi-empirical calculations (computed for R=Me on the PM3 level)

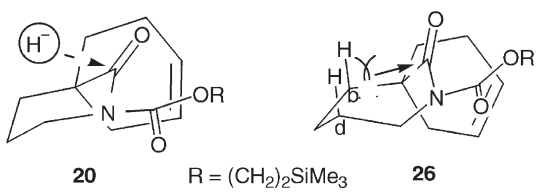
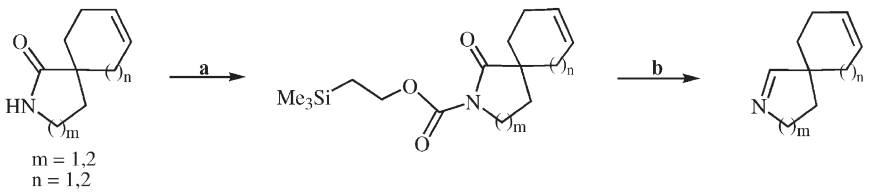
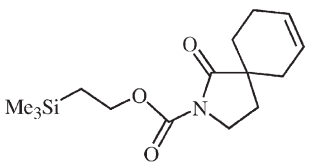
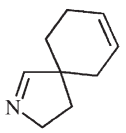
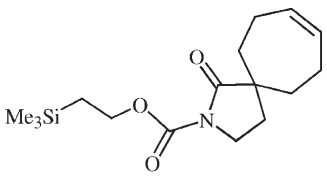
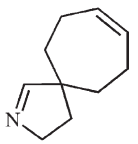
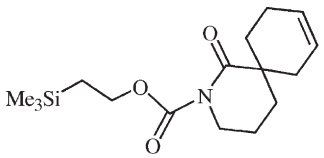
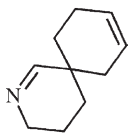
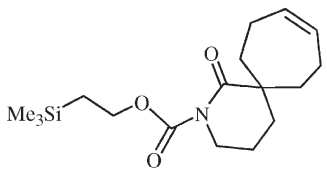
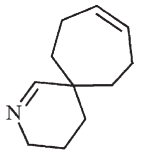


Figure 1. Proposed structures for attack of hydride on the lactam carbonyl group of **20** and **26**.

Table 2. Preparation of spiroimines[a,b]

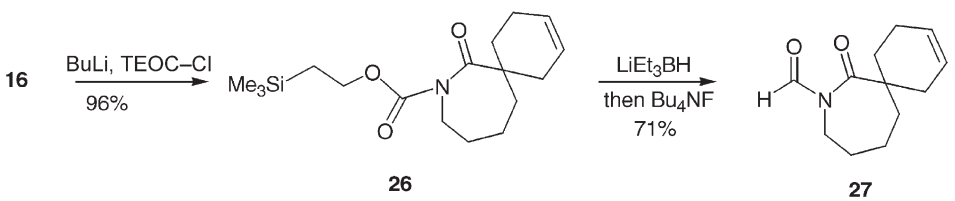


Entry	TEOC lactam (yield %)		Spiroimine (yield %)	
1		**18**, 98%		**22**, 83%
2		**19**, 99%		**23**, 70%
3		**20**, 97%		**24**, 86%
4		**21**, 98%		**25**, 84%

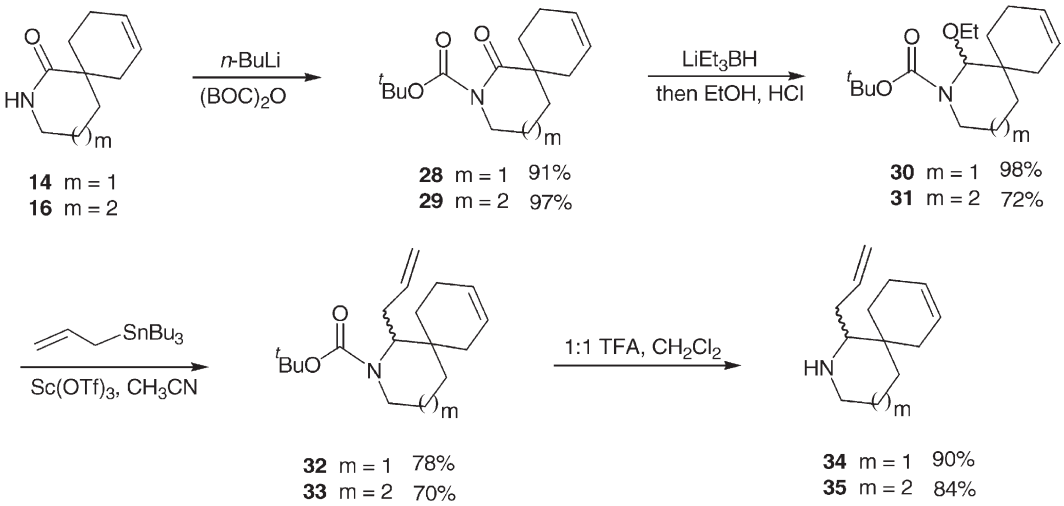
[a] (i) *n*-BuLi (1.05 equiv.), THF, −78 °C; (ii) 2-(trimethylsilyl)ethyl 4-nitrophenyl carbonate (1.15 equiv.), −78 °C to rt.
[b] (i) $LiEt_3H$ (1.2 equiv.), −78 °C then work-up; (ii) Bu_4NF (2 equiv.), THF, rt, 12 h.

suggest that in the seven membered spirolactam (**26**) the carbonyl group experiences considerable steric hindrance due to transannular interactions with the hydrogens on the carbons α and δ to the lactam carbonyl group thus forcing the hydride to attack the more accessible carbonyl group of the carbamate protecting group. However, the six membered ring in spirolactam (**20**) adopts a chair conformation in which the carbonyl group is readily accessible to the incoming hydride source resulting in smooth conversion to the desired spirocyclic imine (**26**) after treatment with tetrabutylammonium fluoride.

The inherent inability to direct hydride addition to the lactam carbonyl group in spirolactam (**26**) rather than the carbonyl group in the TEOC group did not bode well for the future addition of organometallic agents to this carbonyl group as a means to introduce functionality to this carbon in the spirolides (**2**-**5**). This observation prompted protection of the lactam nitrogen with a bulky *tert*-butoxycarbonyl group (BOC) hoping to effect reduction of the lactam rather than the carbamate group (Scheme 3) as reported by Overman et al.[41] on a similar molecule. Successful reduction of the lactam to a hemiaminal then allowed an opportunity for generation and trapping of an acyliminium ion to introduce further functionality at this position as required for the synthesis of the spirolides (**2**-**5**). This methodology could equally be applied to the 6,6-spirolactam ring system (**14**) of gymnodimine (**1**). Our efforts therefore focused on the generation of hemiaminals from spirolactams (**14**) and (**16**) and 'in situ' addition of allylstannane as method to introduce functionality at this position (Scheme 3). Precedent for the regeneration of the spiroimine from the substituted spirolactams was demonstrated from related work by Pradhan et al.[21]



Scheme 2.



Scheme 3.

Protection of spirolactams (**14**) and (**16**) as BOC derivatives (**28**) and (**29**) proceeded uneventfully using *n*-BuLi and *tert*-butyloxycarbonyl anhydride. Subsequent treatment with lithium superhydride effected reduction of the lactam carbonyl group to give hemiaminals (**30**) and (**31**) in 70% yield upon treatment with ethanolic HCl.[41] Reaction of the hemiaminals (**30**) and (**31**) with excess allyltributylstannane in the presence of scandium(III)triflate in acetonitrile at 0 °C effected generation of the acyliminium ion[42] and subsequent conversion to the allylated adducts (**32**) and (**33**). The ^{1}H and ^{13}C NMR spectra of the hemiaminals (**30**), (**31**) and the allylated products (**32**), (**33**) were complicated by the presence of conformers of the two diastereomers due to the restricted rotation imposed by the bulky BOC group. Subsequent removal of the BOC group provided amines (**34**) and (**35**) for which the NMR spectra then only showed the presence of the two diastereomers as a 1:1 mixture.

The successful conversion of spirolactams (**14**) and (**16**) to the allylated adducts (**32**) and (**33**) provides an approach for appendage of functionality to the lactam carbonyl group as required for the synthesis of gymnodimine (**1**) and the spirolides (**2**–**5**). The use of an acyliminium ion intermediate to effect this transformation thus provides an attractive alternative to the addition of an organometallic species to the lactam carbonyl group that would be hampered by the steric bulk imposed by the neighbouring quaternary spiro centre.

In conclusion we have demonstrated that α,α-dialkylated lactams can be utilized in conjunction with ring closing metathesis as an efficient method for the construction of spiroimines. The procedure combines the use of a convenient lactam double alkylation protocol with a highly efficient ring-closing metathesis step. Additionally, a useful method for the reduction of the sterically hindered spirolactams to spirocyclic imines has been extended from the work of Grieco and Kaufmann.[40] This methodology provides access to 6,6-spiroimine (**26**) that is the key pharmacophore in the shellfish toxin gymnodimine (**1**). As part of model studies directed towards the synthesis of the macrolide shellfish toxins, the spirolides (**1**-**5**), 7,6-spirolactam (**16**) underwent scandium triflate promoted allylation of a derived acyliminium ion. Incorporation of this methodology into the synthesis of the spirolides is currently under investigation in our laboratory.

3. Experimental

Melting points were determined using a Kofler hot stage apparatus and are uncorrected. Infrared spectra were recorded on a Perkin–Elmer Spectrum One Fourier-transform infrared spectrophotometer as thin films or Nujol mulls between sodium chloride plates. Proton (^{1}H) nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance 300 (300 MHz) or a Bruker DRX-400 (400 MHz) spectrometer at ambient temperature. Carbon (^{13}C) NMR spectra were recorded on a Bruker Avance 300 (75 MHz) or a Bruker DRX 400 (100 MHz) spectrometer at ambient temperature with complete proton decoupling. All spectra were recorded using $CDCl_3$ as the solvent with reference to residual $CHCl_3$ (^{1}H at 7.26 ppm and ^{13}C at 77.0 ppm). Low resolution mass spectra were recorded on a VG70-SE double focusing magnetic sector mass spectrometer operating with an ionisation potential of 70 eV. High resolution mass spectra were recorded at nominal resolution of 5000 or 10,000 as appropriate. Major fragments are given as percentages relative to the base peak and assigned where possible. Ionisation methods employed were either electron impact or chemical ionisation with ammonia or methane as reagent gas (CI). Fast atom bombardment (FAB) mass spectra were obtained using 3-nitrobenzyl alcohol as the matrix. Flash chromatography was performed using Merck Kieselgel 60 or Riedel-de-Haen Kieselgel S silica gel (both 230–400 mesh) with the indicated solvents. Compounds were visualized under ultraviolet light or by staining with iodine, alkaline permanganate or vanillin in methanolic sulfuric acid. Tetrahydrofuran was distilled from sodium/benzophenone and dichloromethane was distilled from calcium hydride immediately before use.

3.1. General procedure for the dialkylation of lactams

To a stirred solution of the lactam (5 mmol) in dry THF (30 mL) was added dropwise *n*-BuLi (1.6 M solution in

hexane, 3.28 mL, 5.25 mmol) at −78 °C. After stirring for 15 min at −78 °C, trimethylsilyl chloride (0.67 mL, 5.25 mmol) was added dropwise and stirring continued for 30 min while the solution was allowed to warm to 0 °C.

Method A. The reaction mixture was then cooled to −78 °C and transferred (via cannula) to a solution of freshly prepared LDA (5 mmol) in dry THF (20 mL) at −78 °C. After stirring for 30 min at −78 °C, 4-bromo-1-butene (0.53 mL, 5.25 mmol) was added dropwise and stirring continued for 1 h while the solution was allowed to warm to 0 °C. The reaction mixture was then cooled to −78 °C and transferred to a solution of freshly prepared LDA (5.5 mmol) in dry THF (20 mL) at −78 °C. After stirring for 45 min at −78 °C, allyl iodide (0.57 mL, 6.25 mmol) was added dropwise and stirring continued for 3 h while the solution was allowed to warm to 23 °C.

Method B. The reaction mixture was then cooled to −78 °C and transferred (via cannula) to a solution of freshly prepared LDA (11.5 mmol) in dry THF (30 mL) at −78 °C. After stirring for 30 min at −78 °C, 4-bromo-1-butene (1.26 mL, 12.5 mmol) was added dropwise and stirring continued for 4 h while the solution was allowed to warm to 23 °C.

The reaction mixture was quenched by the addition of saturated aqueous NH_4Cl solution and extracted with Et_2O. The combined organic layers were dried over $MgSO_4$. The solvents were removed under reduced pressure and the dialkylated lactam was obtained after purification of the residue by column chromatography using ether or hexane/ether 1:1 as eluant.

3.1.1. 3-Allyl-bis(3-butenyl)-2-pyrrolidinone (6). 74% Yield; colorless oil; IR ν_{max}/cm^{-1} 3231, 3076, 2914, 1693, 1450, 1282, 996, 912; ^1H NMR (300 MHz, $CDCl_3$) δ 6.53 (bs, 1H), 5.87–5.72 (m, 2H), 5.15–4.92 (m, 4H), 3.29–3.24 (m, 2H), 2.38–1.94 (m, 6H), 1.70–1.53 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.4, 138.2, 133.9, 118.4, 114.6, 46.3, 41.2, 39.1, 35.9, 30.0, 28.6; MS (EI) *m/z* 179 (5%, $[M]^+$), 125 (100); HRMS Calcd for $C_{11}H_{17}NO$ 179.1310; found, 179.1305.

3.1.2. 3,3-Bis(3-butenyl)-2-pyrrolidinone (7). 71% Yield; colorless oil; IR ν_{max}/cm^{-1} 3223, 3077, 2935, 1692, 1453, 1283, 994, 909; ^1H NMR (300 MHz, $CDCl_3$) δ 6.79 (bs, 1H), 5.86–5.72 (m, 2H), 5.05–4.90 (m, 4H), 3.28 (t, 2H, *J*=7.1 Hz), 2.18–1.96 (m, 6H), 1.65–1.55 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.7, 138.3, 114.5, 46.2, 39.1, 35.7, 30.8, 28.5; MS (EI) *m/z* 193 (1%, $[M]^+$), 139 (32), 98 (100); HRMS Calcd for $C_{12}H_{19}NO$ 193.1467; found, 193.1465.

3.1.3. 3-Allyl-3-(3-butenyl)tetrahydro-2(1*H*)-pyridinone (8). 81% Yield; colorless oil; IR ν_{max}/cm^{-1} 3278, 3074, 2942, 1659, 1489, 1448, 997, 911; ^1H NMR (300 MHz, $CDCl_3$) δ 6.00 (bs, 1H), 5.84–5.73 (m, 2H), 5.09–4.91 (m, 4H), 3.28–3.23 (m, 2H), 2.53–2.47 (m, 1H), 2.25–2.19 (m, 1H), 2.15–1.99 (m, 2H), 1.84–1.67 (m, 5H), 1.57–1.47 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.4, 138.6, 134.3, 118.1, 114.4, 44.4, 43.0, 42.7, 37.6, 29.3, 28.7, 19.7; MS (EI) *m/z* 193 (4%, $[M]^+$), 139 (100); HRMS Calcd for $C_{12}H_{19}NO$ 193.1467; found, 193.1468.

3.1.4. 3,3-Bis(3-butenyl)tetrahydro-2(1*H*)-pyridinone (9). 78% Yield; colorless oil; IR ν_{max}/cm^{-1} 2946, 2869, 1654, 1488, 1265, 915, 940; ^1H NMR (300 MHz, $CDCl_3$) δ 6.11 (bs, 1H), 5.84–5.74 (m, 2H), 5.03–4.90 (m, 4H), 3.28–3.24 (m, 2H), 2.14–1.98 (m, 4H), 1.82–1.71 (m, 6H), 1.59–1.52 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.6, 138.6, 114.4, 44.2, 42.6, 37.7, 29.7, 28.6, 19.8; MS (EI) *m/z* 207 (1%, $[M]^+$), 153 (20), 112 (100); HRMS Calcd for $C_{13}H_{21}NO$ 207.1623; found, 207.1624.

3.1.5. 3-Allyl-3-(3-butenyl)-2-azepanone (10). 67% Yield; colorless oil; IR ν_{max}/cm^{-1} 3281, 3073, 2868, 1650, 1478, 1435, 1411, 1362, 1281, 995, 910; ^1H NMR (300 MHz, $CDCl_3$) δ 5.98 (bs, 1H), 5.86–5.76 (m, 2H), 5.09–4.91 (m, 4H), 3.31–3.23 (m, 1H), 3.21–3.13 (m, 1H), 2.48–2.43 (m, 1H), 2.36–2.31 (m, 1H), 2.17–2.07 (m, 1H), 2.04–1.95 (m, 1H), 1.80–1.54 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.5, 138.7, 134.9, 117.7, 114.3, 47.8, 42.2, 41.3, 34.3, 32.6, 29.1, 28.3, 23.7; MS (EI) *m/z* 207 (5%, $[M]^+$), 153 (100); HRMS Calcd for $C_{13}H_{21}NO$ 207.1623; found, 207.1618.

3.1.6. 3,3-Bis(3-butenyl)-2-azepanone (11). 77% Yield; colorless oil; IR ν_{max}/cm^{-1} 2931, 2869, 1651, 1478, 1460, 1408, 1282, 995, 908; ^1H NMR (300 MHz, $CDCl_3$) δ 6.02 (bs, 1H), 5.90–5.77 (m, 2H), 5.06–4.92 (m, 4H), 3.25–3.19 (m, 2H), 2.17–1.59 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.7, 138.9, 114.3, 47.7, 42.3, 35.5, 32.5, 29.1, 28.5, 23.7; MS (EI) *m/z* 221 (1%, $[M]^+$), 167 (22), 126 (100); HRMS Calcd for $C_{14}H_{23}NO$ 221.1780; found, 221.1776.

3.2. General procedure for the metathesis reaction

To a stirred solution of dialkylated lactam (3 mmol) in dry dichloromethane (30 mL) was added benzylidene-bis(tricyclohexylphosphine)-dichlororuthenium (0.12 g, 0.15 mmol) at 23 °C and the reaction mixture stirred for 3 h. DMSO (0.5 mL) was added and stirring continued for 12 h. The solvents were removed under reduced pressure and the bicyclic lactam was obtained after purification of the residue by column chromatography using ether or hexane/ether 1:1 as eluant.

3.2.1. 2-Azaspiro[4.5]dec-7-en-1-one (12). 86% Yield; colorless oil; IR ν_{max}/cm^{-1} 2930, 2898, 1680, 1431, 1293, 810; ^1H NMR (300 MHz, $CDCl_3$) δ 6.88 (bs, 1H), 5.75–5.63 (m, 2H), 3.34 (t, 2H, *J*=6.8 Hz), 2.41–2.31 (m, 1H), 2.24–1.80 (m, 6H), 1.57–1.49 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.0, 126.3, 124.6, 41.9, 38.9, 32.1, 31.9, 28.1, 22.0; MS (EI) *m/z* 151 (100%, $[M]^+$), 122 (28), 93 (25), 79 (35); HRMS Calcd for $C_9H_{13}NO$ 151.0997; found, 151.0996.

3.2.2. 2-Azaspiro[4.6]undec-8-en-1-one (13). 93% Yield; colorless oil; IR ν_{max}/cm^{-1} 3015, 2932, 2845, 1652, 1444, 1292, 1284, 1073, 711; ^1H NMR (300 MHz, $CDCl_3$) δ 6.07 (bs, 1H), 5.78–5.68 (m, 2H), 3.30 (t, 2H, *J*=6.8 Hz), 2.42–2.31 (m, 2H), 2.19–1.87 (m, 6H), 1.63–1.55 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.3, 131.4, 46.5, 38.6, 33.9, 33.4, 24.4; MS (EI) *m/z* 165 (15%, $[M]^+$), 98 (100); HRMS Calcd for $C_{10}H_{15}NO$ 165.1154; found, 165.1155.

3.2.3. 2-Azaspiro[5.5]undec-8-en-1-one (14). 90% Yield; colorless oil; IR ν_{max}/cm^{-1} 2948, 1650, 1489, 1265, 729,

704; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.93 (bs, 1H), 5.68–5.58 (m, 2H), 3.29–3.26 (m, 2H), 2.60–2.56 (m, 1H), 2.14–1.54 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.2, 125.3, 124.6, 42.6, 39.7, 33.3, 30.1, 28.9, 21.3, 19.0; MS (EI) *m/z* 165 (100%, $[M]^+$), 136 (80); HRMS Calcd for $C_{10}H_{15}NO$ 165.1154; found, 165.1155.

3.2.4. 2-Azaspiro[5.6]dodec-9-en-1-one (15). 95% Yield; colorless oil; IR ν_{max}/cm^{-1} 3017, 2941, 2870, 1649, 1488, 1314, 922, 745, 722; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.83 (bs, 1H), 5.67–5.60 (m, 2H), 3.31–3.26 (m, 2H), 2.41–2.33 (m, 2H), 2.23–2.07 (m, 4H), 1.82–1.73 (m, 4H), 1.66–1.57 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.7, 130.7, 43.5, 42.5, 36.0, 31.7, 24.4, 18.7; MS (EI) *m/z* 179 (7%, $[M]^+$), 112 (100); HRMS Calcd for $C_{11}H_{17}NO$ 179.1310; found, 179.1310.

3.2.5. 8-Azaspiro[5.6]dodec-2-en-7-one (16). 88% Yield; colorless oil; IR ν_{max}/cm^{-1} 2932, 1642, 1478, 1271, 723, 701; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.06 (bs, 1H), 5.67–5.63 (m, 2H), 3.36–3.16 (m, 2H), 2.76–2.64 (m, 1H), 2.16–1.51 (m, 11H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.0, 125.3, 125.2, 43.4, 42.7, 33.7, 31.8, 29.6, 27.4, 24.4, 22.3; MS (EI) *m/z* 179 (100%, $[M]^+$), 150 (50); HRMS Calcd for $C_{11}H_{17}NO$ 179.1310; found, 179.1308.

3.2.6. 2-Azaspiro[6.6]tridec-10-en-1-one (17). 92% Yield; colorless oil; IR ν_{max}/cm^{-1} 3053, 2930, 2844, 1641, 1434, 1265, 737, 704; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.01 (bs, 1H), 5.68–5.59 (m, 2H), 3.27–3.21 (m, 2H), 2.41–2.06 (m, 6H), 1.81–1.57 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.1, 130.9, 48.0, 42.8, 34.5, 33.8, 29.5, 24.2, 24.15; MS (EI) *m/z* 193 (6%, $[M]^+$), 126 (100); HRMS Calcd for $C_{12}H_{19}NO$ 193.1467; found, 193.1465.

3.3. General procedure for the TEOC-protection of spirolactams

To a stirred solution of the bicyclic lactam (3 mmol) in dry THF (30 mL) was added dropwise a 1.6 M solution of *n*-BuLi in hexane (1.97 mL, 3.15 mmol) at −78 °C. After stirring for 30 min at −78 °C a solution of 2-(trimethylsilyl)ethyl 4-nitrophenyl carbonate (0.98 g, 3.45 mmol) in dry THF (5 mL) was added dropwise and stirring continued for 1.5 h while the solution was allowed to warm up to 23 °C. The reaction mixture was quenched by the addition of saturated aqueous NH_4Cl solution and extracted with Et_2O. The combined organic layers were dried over $MgSO_4$. The solvents were removed under reduced pressure and the TEOC protected lactam was obtained after purification of the residue by column chromatography using hexane/ether 10:3 as eluant.

3.3.1. 2-(Trimethylsilyl)ethyl 1-oxo-2-azaspiro[4.5]dec-7-ene-2-carboxylate (18). 98% Yield; colorless oil; IR ν_{max}/cm^{-1} 2953, 2933, 2899, 1752, 1699, 1304, 1249, 1063, 838, 766; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.73–5.61 (m, 2H), 4.35–4.30 (m, 2H), 3.77–3.65 (m, 2H), 2.41–2.33 (m, 1H), 2.22–1.98 (m, 2H), 1.92–1.85 (m, 4H), 1.58–1.51 (m, 1H), 1.13–1.08 (m, 2H), 0.04 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.2, 152.1, 126.2, 123.9, 65.1, 44.5, 42.9, 32.0, 28.5, 28.1, 21.7, 17.5, −1.9; MS (EI) *m/z* 295 (1%, $[M]^+$), 267 (42), 73 (100); HRMS Calcd for $C_{15}H_{25}NO_3Si$ 295.1604; found, 295.1607.

3.3.2. 2-(Trimethylsilyl)ethyl 1-oxo-2-azaspiro[4.6]undec-8-ene-2-carboxylate (19). 99% Yield; colorless oil; IR ν_{max}/cm^{-1} 2961, 2923, 1748, 1710, 1303, 1250, 1063, 939, 836, 766; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.74–5.67 (m, 2H), 4.34–4.30 (m, 2H), 3.68 (t, 2H, J=7.0 Hz), 2.42–2.32 (m, 2H), 2.14–2.04 (m, 2H), 1.99–1.91 (m, 4H), 1.64–1.58 (m, 2H), 1.13–1.08 (m, 2H), 0.03 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.5, 152.2, 131.1, 65.1, 49.0, 42.7, 33.9, 30.3, 24.8, 17.6, −1.6; MS (EI) *m/z* 310 (1%), 281 (2), 214 (100), 154 (42); HRMS Calcd for $C_{16}H_{27}NO_3Si$ 309.1760; could not be detected.

3.3.3. 2-(Trimethylsilyl)ethyl 1-oxo-2-azaspiro[5.5]undec-8-ene-2-carboxylate (20). 97% Yield; colorless oil; IR ν_{max}/cm^{-1} 3025, 2952, 2899, 1769, 1713, 1379, 1295, 1268, 1162, 1049, 944, 860, 838; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.69–5.58 (m, 2H), 4.33–4.29 (m, 2H), 3.76–3.60 (m, 2H), 2.65–2.56 (m, 1H), 2.10–1.62 (m, 9H), 1.12–1.07 (m, 2H), 0.03 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.8, 155.3, 125.4, 124.4, 65.4, 47.4, 43.3, 33.6, 30.7, 29.7, 21.6, 19.4, 17.5, −1.6; MS (EI) *m/z* 309 (1%, $[M]^+$), 281 (30), 73 (100); HRMS Calcd for $C_{16}H_{27}NO_3Si$ 309.1760; found, 309.1763.

3.3.4. 2-(Trimethylsilyl)ethyl 1-oxo-2-azaspiro[5.6]dodec-9-ene-2-carboxylate (21). 98% Yield; colorless oil; IR ν_{max}/cm^{-1} 3015, 2952, 1768, 1714, 1379, 1274, 1160, 935, 860, 838; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.67–5.60 (m, 2H), 4.33–4.28 (m, 2H), 3.67 (t, 2H, J=5.9 Hz), 2.40–2.04 (m, 6H), 1.85–1.76 (m, 4H), 1.68–1.60 (m, 2H) 1.11–1.07 (m, 2H), 0.03 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.0, 155.4, 130.6, 65.3, 47.5, 47.3, 35.9, 32.6, 24.2, 19.2, 17.5, −1.6; MS (EI) *m/z* 323 (1%), 228 (90), 73 (100); HRMS Calcd for $C_{17}H_{29}NO_3Si$ 323.1917; found, 323,1911.

3.4. General procedure for the reduction of TEOC protected lactams

To a stirred solution of the TEOC protected lactam (1 mmol) in dry THF (10 mL) was added dropwise a 1 M solution of $LiEt_3BH$ in THF (1.2 mL, 1.2 mmol) at −78 °C. After stirring for 45 min at −78 °C the reaction mixture was quenched by dropwise addition of water followed by aqueous work up and extraction of the aqueous phase with Et_2O. The combined organic layers were dried over $MgSO_4$ and the solvents removed under reduced pressure. The crude residue was dissolved in THF (10 mL) and treated with a 1 M solution of tetrabutylammonium fluoride in THF (2 mL, 2 mmol). After stirring for 12 h at 23 °C toluene (10 mL) was added and all solvents removed under reduced pressure. The spiroimine was obtained after purification of the residue by column chromatography using ether as eluant.

3.4.1. 2-Azaspiro[4.5]deca-1,7-diene (22). 83% Yield; colorless oil; IR ν_{max}/cm^{-1} 3019, 2918, 2839, 1650, 1435, 1351, 1257, 1206, 921; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (bs, 1H), 5.74–5.61 (m, 2H), 3.86 (t, 2H, J=7.1 Hz), 2.14–2.04 (m, 3H), 1.95–1.86 (m, 1H), 175–1.63 (m, 3H), 1.53–1.47 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5, 126.8, 124.8, 59.8, 34.4, 33.1, 30.2, 29.8, 22.7; MS (EI) *m/z* 135 (85%, $[M]^+$), 80 (100); HRMS Calcd for $C_9H_{13}N$ 135.1048; found, 135.1047.

3.4.2. 2-Azaspiro[4.6]undeca-1,8-diene (23). 70% Yield; colorless oil; IR ν_{max}/cm^{-1} 3017, 2919, 2847, 1690, 1443, 1284, 1267, 1053, 921, 899, 729; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38 (bs, 1H), 5.74 (t, 2H, J=3.1 Hz), 3.83 (dt, 2H, J_d=2.0 Hz, J_t=7.1 Hz), 2.22–2.15 (m, 4H), 1.73–1.64 (m, 4H), 1.58–1.51 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9, 131.5, 59.6, 34.4, 33.8, 24.9, 24.2; MS (EI) m/z 149 (75%, $[M]^+$), 93 (100), 79 (90); HRMS Calcd for $C_{10}H_{15}N$ 149.1204; found, 149.1201.

3.4.3. 2-Azaspiro[5.5]undeca-1,8-diene (24). 86% Yield; colorless oil; IR ν_{max}/cm^{-1} 3023, 2923, 2852, 1649, 1438, 1220, 1047, 923; ^1H NMR (300 MHz, $CDCl_3$) δ 7.52 (bs, 1H), 5.73–5.57 (m, 2H), 3.61–3.43 (m, 2H), 2.10–1.18 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6, 126.3, 124.0, 49.9, 34.7, 33.4, 31.1, 29.5, 21.2, 19.0; MS (EI) m/z 149 (96%, $[M]^+$), 120 (100); HRMS Calcd for $C_{10}H_{15}N$ 149.1204; found, 149.1204.

3.4.4. 2-Azaspiro[5.6]dodeca-1,9-diene (25). 84% Yield; colorless oil; IR ν_{max}/cm^{-1} 3014, 2919, 2851, 1650, 1453, 1343, 1259, 1052, 973, 924, 899, 717; ^1H NMR (300 MHz, $CDCl_3$) δ 7.67 (bs, 1H), 5.68 (t, 2H, J=3.0 Hz), 3.57–3.42 (m, 2H), 2.25–2.10 (m, 4H), 1.72–1.54 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 131.0, 49.8, 36.0, 35.3, 30.0, 23.4, 18.9; MS (EI) m/z 163 (81%, $[M]^+$), 134 (100), 96 (72); HRMS Calcd for $C_{11}H_{17}N$ 163.1361; found, 163.1356.

3.5. General procedure for the Boc-protection of spirolactams

To a stirred solution of the bicyclic lactam (3 mmol) in dry THF (30 mL) was added dropwise a 1.6 M solution of *n*-BuLi in hexane (1.97 mL, 3.15 mmol) at −78 °C. After stirring for 30 min at −78 °C a solution of *tert*-butyloxycarbonyl anhydride (0.79 g, 3.60 mmol) in dry THF (5 mL) was added dropwise and stirring continued for 1.5 h while the solution was allowed to warm up to 23 °C. The reaction mixture was quenched by the addition of saturated aqueous NH_4Cl solution and extracted with Et_2O. The combined organic layers were dried over $MgSO_4$. The solvents were removed under reduced pressure and the Boc protected lactam was obtained after purification of the residue by column chromatography using hexane/ether 10:2 as eluant.

3.5.1. *tert*-Butyl 1-oxo-2-azaspiro[5.5]undec-8-ene-2-carboxylate (28). 91% Yield; colorless oil; IR ν_{max}/cm^{-1} 2977, 2936, 1766, 1714, 1367, 1296, 1277, 1149; ^1H NMR (300 MHz, $CDCl_3$) δ 5.69–5.57 (m, 2H), 3.69–3.54 (m, 2H), 2.64–2.55 (m, 1H), 2.07–1.61 (m, 9H), 1.50 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.8, 153.7, 125.4, 124.6, 82.4, 47.3, 43.2, 33.6, 30.7, 29.9, 28.0, 21.6, 19.4; MS (EI) m/z 265 (1%, $[M]^+$), 209 (87), 57 (100); HRMS Calcd for $C_{15}H_{23}NO_3$ 265.1678; found, 265.1678.

3.5.2. *tert*-Butyl 7-oxo-8-azaspiro[5.6]dodec-2-ene-8-carboxylate (29). 97% Yield; colorless oil; IR ν_{max}/cm^{-1} 2976, 2931, 1753, 1713, 1367, 1317, 1296, 1277, 1257, 1151; ^1H NMR (300 MHz, $CDCl_3$) δ 5.68–5.59 (m, 2H), 3.66–3.54 (m, 2H), 2.63–2.54 (m, 1H), 2.13–1.90 (m, 3H), 1.74–1.48 (m, 8H), 1.44 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.4, 154.0, 126.0, 125.6, 81.4, 47.5, 44.4, 33.7, 32.8, 29.9, 28.0, 26.3, 23.2, 22.3; MS (EI) m/z 279 (1%, $[M]^+$), 223 (54), 57 (100); HRMS Calcd for $C_{16}H_{25}NO_3$ 279.1834; found, 279.1831.

3.6. General procedure for the reduction of BOC-protected lactams

To a stirred solution of the Boc protected lactam (1 mmol) in dry THF (10 mL) was added dropwise a 1 M solution of $LiEt_3BH$ in THF (3 mL, 3 mmol) at −78 °C. After stirring for 30 min at −78 °C the reaction mixture was quenched by the addition of a solution of conc. HCl (1 mL) in ethanol (10 mL) and warmed up to 23 °C. After addition of ether (50 mL) followed by aqueous work up and extraction of the aqueous phase with Et_2O, the combined organic layers were dried over $MgSO_4$ and the solvents removed under reduced pressure. The hemiaminal was obtained after purification of the residue by column chromatography using hexane/ether 10:2 as eluant.

3.6.1. *tert*-Butyl 1-ethoxy-2-azaspiro[5.5]undec-8-ene-2-carboxylate (30). 98% Yield; colorless oil (mixture of diastereomers and rotamers);[†] IR ν_{max}/cm^{-1} 2973, 2930, 1700, 1654, 1451, 1414, 1364, 1281, 1250, 1156, 1078; ^1H NMR (300 MHz, $CDCl_3$) δ 5.72–5.53 (m, 2H), 5.16, 5.08, 5.06 and 4.93 (each s, 1H), 3.97–3.89 and 3.81–3.74 (2m, 1H), 3.52–3.25 (m, 2H), 2.99–2.81 (m, 1H), 2.12–1.92 (m, 3H), 1.83–1.36 (m, 16H), 1.16 and 1.15 (2q, 3H, J=6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.5, 155.2, 126.7, 126.6, 125.9, 125.7, 125.2, 125.0, 124.9, 124.8, 86.1, 85.7, 84.1, 83.8, 79.5, 79.4, 79.3, 62.6, 62.1, 62.0, 38.8, 38.6, 37.4, 37.3, 35.4, 35.3, 35.2, 35.1, 32.0, 31.9, 31.1, 31.0, 30.5, 28.4, 27.9, 27.4, 27.0, 26.9, 21.8, 21.7, 20.8, 20.7, 20.5, 20.4, 15.1, 15.0, 14.8; MS (EI) m/z 295 (1%, $[M]^+$), 193 (100), 57 (80); HRMS Calcd for $C_{17}H_{29}NO_3$ 295.2147; found, 295.2147.

3.6.2. *tert*-Butyl 7-ethoxy-8-azaspiro[5.6]dodec-2-ene-8-carboxylate (31). 72% Yield; colorless oil (mixture of diastereomers and rotamers);[†] IR ν_{max}/cm^{-1} 2973, 2928, 1696, 1451, 1414, 1365, 1330, 1211, 1166, 1130, 1081; ^1H NMR (300 MHz, $CDCl_3$) δ 5.73–5.49 (m, 2H), 5.22, 5.15, 5.08 and 4.94 (each s, 1H), 3.53–3.15 (m, 4H), 2.09–1.36 (m, 21H), 1.17–1.13 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.2, 155.8, 126.6, 126.5, 126.0, 125.5, 125.4, 125.1, 90.4, 89.8, 86.9, 86.5, 79.5, 79.4, 79.1, 79.0, 63.0, 62.8, 62.6, 62.4, 40.4, 40.3, 40.2, 39.9, 39.7, 39.2, 36.2, 35.9, 32.9, 32.5, 32.2, 31.9, 31.7, 31.5, 28.5, 28.4, 28.1, 27.4, 27.2, 25.7, 25.4, 25.2, 22.6, 21.9, 21.8, 20.5, 20.3, 19.9, 19.7, 14.9, 14.8, 14.7; MS (EI) m/z 309 (1%, $[M]^+$), 207 (75), 57 (100); HRMS Calcd for $C_{18}H_{31}NO_3$ 309.2304; found, 309.2302.

3.7. General procedure for the allylation reaction

To a stirred solution of the hemiaminal (0.4 mmol) in dry acetonitrile (5 mL) was added allyltributylstannane (0.37 mL, 1.2 mmol) and scandium(III)triflate (20 mg, 0.04 mmol) at 0 °C. The reaction was monitored by TLC (hexane/ether 10:2) and stirred at 0 °C until completion

[†] The presence of both diastereomers and rotamers afforded complex ^1H and ^{13}C NMR spectra with overlapping signals that are only reported once.

(8–12 h). In some cases further addition of scandium(III)-triflate (20 mg, 0.04 mmol) after 6 h was necessary to obtain complete reaction. The reaction mixture was evaporated under reduced pressure and the Boc-protected allylated amine was obtained after purification of the residue by column chromatography using hexane/ether 10:2 as eluant.

3.7.1. *tert*-Butyl 1-allyl-2-azaspiro[5.5]undec-8-ene-2-carboxylate (32). 78% Yield; colorless oil (mixture of diastereomers and rotamers);† IR ν_{max}/cm^{-1} 2974, 2930, 2863, 1693, 1417, 1364, 1248, 1176, 1159, 1147, 909; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.77–5.50 (m, 3H), 5.06–4.93 (m, 2H), 4.12–4.03 (m, 1H), 3.94–3.84 (m, 1H), 2.77–2.62 (m, 1H), 2.51–2.35 (m, 1H), 2.29–1.20 (m, 20H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.7, 155.6, 135.9, 135.8, 135.5, 135.4, 126.6, 126.5, 125.9, 125.7, 125.4, 124.3, 124.2, 116.4, 116.3, 115.9, 79.0, 78.9, 78.7, 58.2, 56.9, 54.8, 53.9, 38.9, 38.6, 37.5, 37.1, 36.4, 36.3, 34.1, 34.0, 33.8, 33.6, 33.5, 31.9, 31.3, 30.7, 30.4, 30.3, 30.2, 29.7, 28.6, 28.5, 28.4, 27.3, 26.9, 22.2, 22.1, 21.0, 20.9, 20.6, 20.5; MS (EI) *m/z* 291 (1%, [M]$^+$), 194 (100), 150 (34); HRMS (CI) Calcd for $C_{18}H_{30}NO_2$ (M+H) 292.2276; found, 292.2275 ([M+H]$^+$).

3.7.2. *tert*-Butyl 7-allyl-8-azaspiro[5.6]dodec-2-ene-8-carboxylate (33). 70% Yield; colorless oil (mixture of diastereomers and rotamers);† IR ν_{max}/cm^{-1} 2973, 2927, 2865, 1688, 1414, 1364, 1166, 1135, 909; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.83–5.48 (m, 3H), 5.06–4.92 (m, 2H), 4.33–4.20 and 4.03–3.90 (each m, 1H), 3.79–3.46 (m, 1H), 2.97–2.76 (m, 1H), 2.38–1.17 (m, 23H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.7, 156.4, 156.2, 136.8, 136.4, 136.3, 136.0, 135.8, 135.6, 135.5, 126.8, 126.7, 125.9, 125.8, 125.7, 124.8, 124.7, 116.6, 116.4, 116.3, 116.2, 116.0, 115.9, 79.1, 79.0, 78.6, 63.0, 61.4, 58.5, 58.0, 41.6, 41.2, 41.0, 40.9, 39.3, 39.1, 38.4, 37.4, 36.9, 36.5, 35.1, 34.2, 34.1, 32.8, 32.2, 32.0, 31.4, 31.3, 31.1, 30.8, 30.7, 30.4, 30.3, 29.7, 29.5, 29.2, 29.0, 28.6, 28.5, 28.3, 27.5, 26.7, 26.1, 26.0, 22.5, 22.4, 22.3, 20.7, 20.3, 20.1, 19.9; MS (EI) *m/z* 305 (1%, [M]$^+$), 208 (100), 57 (95); HRMS Calcd for $C_{19}H_{31}NO_2$ 305.2355; found, 305.2357.

3.8. General procedure for the Boc-deprotection

To a stirred solution of the Boc-protected amine (0.3 mmol) in DCM (3 mL) was added TFA (3 mL). After stirring for 30 min at 23 °C toluene (20 mL) was added and the reaction mixture evaporated under reduced pressure. The spiroamine was obtained after purification of the residue by column chromatography using hexane/DCM/MeOH/Et_3N 10:20:4:0.2 as eluant.

3.8.1. 1-Allyl-2-azaspiro[5.5]undec-8-ene (34). 90% Yield; colorless oil (mixture of diastereomers);† IR ν_{max}/cm^{-1} 3019, 2927, 2844, 1451, 1435, 1313, 1132, 913, 758; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.78–5.68 (m, 1H), 5.64–5.55 (m, 2H), 5.12–5.04 (m, 2H), 3.04–2.98 (m, 1H), 2.62–2.54 (m, 1H), 2.41–2.24 (m, 2H), 2.13–1.12 (m, 11H), 1.01–0.87 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.2, 137.1, 126.1, 125.9, 125.8, 125.3, 117.5, 117.3, 64.9, 62.5, 47.0, 46.5, 35.6, 34.0, 33.9, 33.1, 31.7, 31.4, 27.2, 23.4, 22.4, 22.2, 22.0; MS (EI) *m/z* 192 (30%, [M+H]$^+$), 150 (100); HRMS (CI) Calcd for $C_{13}H_{22}N$ (M+H) 192.1752; found, 192.1751 ([M+H]$^+$).

3.8.2. 7-Allyl-8-azaspiro[5.6]dodec-2-ene (35). 84% Yield; colorless oil (mixture of diastereomers);† IR ν_{max}/cm^{-1} 3019, 2925, 2854, 1448, 1438, 1152, 992, 913; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.83–5.53 (m, 3H), 5.13–5.01 (m, 2H), 3.17–3.02 (m, 1H), 2.58–2.39 (m, 1H), 2.34–2.15 (m, 2H), 2.10–1.22 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.6, 137.5, 127.2, 126.3, 125.9, 125.7, 117.2, 117.0, 67.8, 67.6, 52.3, 50.0, 38.1, 37.8, 35.8, 35.4, 35.1, 34.6, 32.7, 32.6, 31.7, 31.5, 29.7, 27.8, 22.9, 21.9, 21.2, 21.15; MS (EI) *m/z* 205 (20%, [M]$^+$), 164 (100); HRMS Calcd for $C_{14}H_{23}N$ 205.1831; found, 179.1825.

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