A Facile Synthesis of a Spironitrone and a Study of Its Cycloaddition and Nucleophilic Addition Reactions

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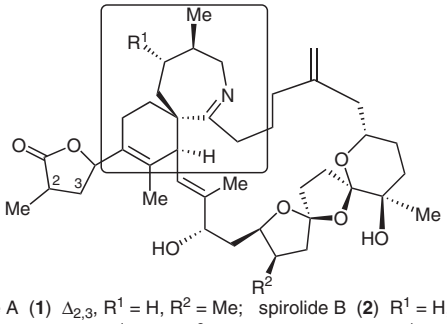
Abstract: The synthesis of spironitrone **5** via microwave-assisted intramolecular alkylation of bromo oxime **10** is reported. The bromo oxime is prepared by alkylation of methyl cyclohexanecarboxylate with 1,4-dibromobutane followed by conversion of the methyl ester to an oxime. Spironitrone **5** undergoes facile 1,3-dipolar cycloaddition to a range of olefins to form a range of spirocyclic isoxazolidines. Nucleophilic addition of several Grignard reagents to spironitrone **5** provided access to a series of alkyl-substituted spirohydroxylamines.

Key words: 1,3-dipolar cycloaddition, spironitrones, microwave, Grignard reagents

The 1,3-dipolar cycloaddition of nitrones to dipolarophiles is a reaction of much utility in alkaloid synthesis, yielding isoxazolidines with up to three new defined carbon stereocentres in a single step. A variety of compounds can then accessed by synthetic manipulation of the isoxazolidine cycloadducts.[1]Specifically, reduction of the isoxazolidine ring proceeds with retention of configuration affording β-amino alcohols of defined stereochemistry,[2] while oxidation yields nitrones that may be further functionalised. As part of a programme aimed at the synthesis of a variety of spirocyclic scaffolds related to the core heterocyclic framework of the 7,6-spiroimine unit of the spirolide family of shellfish toxins[3] (Figure 1), we herein report the facile synthesis of 7,6-spironitrone **1** together with a study of its 1,3-cycloaddition to a range of dipolarophiles (Scheme 1). Additionally, nucleophilic addition of a series of organometallic agents to spironitrone



spirolide A (**1**) $\Delta_{2,3}$, R^1 = H, R^2 = Me; spirolide B (**2**) R^1 = H, R^2 = Me
spirolide C (**3**) $\Delta_{2,3}$, R^1 = Me, R^2 = Me; spirolide D (**4**) R^1 = Me, R^2 = Me

Figure 1 Structure of the spirolides

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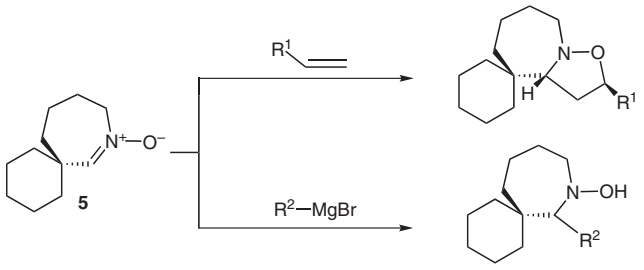
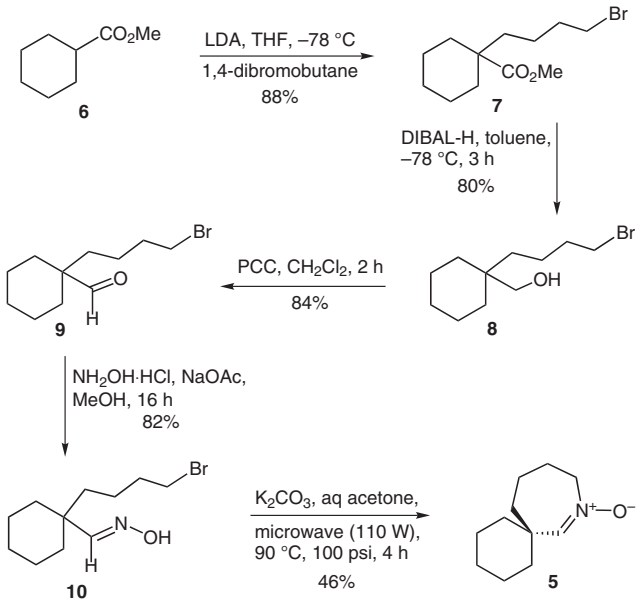


Scheme 1

1 has been investigated, providing a range of spirocyclic hydroxylamines for pharmacological evaluation. Closely related spironitrones have provided key intermediates for construction of the core structures of the bicyclic alkaloid pinnaic acid[4] and the ABC ring system of the alkaloid upenamide[5] lends itself well to the application of spironitrone cycloaddition chemistry.

Spironitrone **5** was easily accessed in five steps (Scheme 2) via monoalkylation of methyl cyclohexanecarboxylate **6** with lithium diisopropylamide (LDA) and quenching with 1,4-dibromobutane to afford bromide **7** in 88% yield. Conversion of the methyl ester to an aldehyde in one step proved problematic. However, conversion of the methyl ester to an alcohol **8** using diisobutylaluminum hydride (DIBAL-H) in toluene and thence to aldehyde **9**



Scheme 2 Synthesis of spironitrone **5**

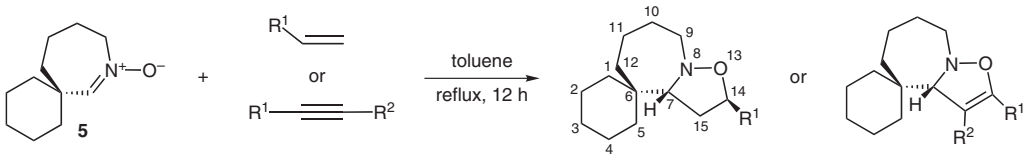
using pyridinium chlorochromate (PCC), allowed preparation of bromo oxime **10**. Formation of spironitrone **5** from oxime **10** under thermal conditions was plagued by a slow cyclisation rate and the decomposition of the spironitrone product during the long reaction time. After considerable experimentation, the key intramolecular cyclisation to spironitrone **5** was effected in acetone–water (4:1) in the presence of potassium carbonate using a CEM Discovery microwave reactor (100 W, 90 °C and 100 psi for 4 h).

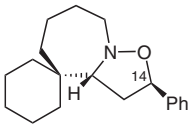
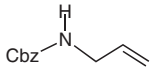
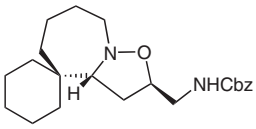
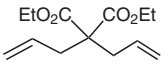
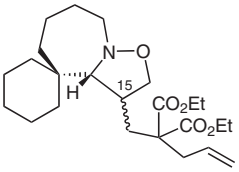
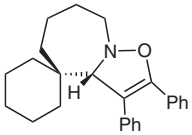
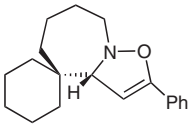
Spironitrone **5** was used immediately as a 1,3-dipole for cycloaddition reactions as it was unstable at room temperature and underwent decomposition upon storage in the fridge for a few days. The synthetic utility of spironitrone **5** was investigated by examining its 1,3-dipolar cycloaddition with several diverse dipolarophiles (Table 1).

The 1,3-dipolar additions under investigation were based on work reported by Ishibashi et al.[6] using simple cyclic nitrones as 1,3-dipoles. Spironitrone **5** failed to undergo cycloaddition with 1,3-dipolarophiles bearing electron-withdrawing groups such as maleic anhydride, maleimide, dimethyl maleate, and cyclohexenone. Gratifyingly, heating spironitrone **5** with an electron-rich dipolarophile, styrene **11** (3 equiv), in toluene for 12 hours, afforded a 7:1 mixture of the major *exo*-cycloadduct **16** together with the minor *endo*-cycloadduct (epimeric at C14). An X-ray crystal structure[7] of the major *exo*-adduct **16** (Figure 2) confirmed both the regiochemical outcome of the cycloaddition reaction and the relative stereochemistry of the major product. Thus, the X-ray crystal structure of cycloadduct clearly established that the bridgehead proton was *syn* to the phenyl group.[7]

Reaction of CBz-protected allylamine **12** with spironitrone **5** under similar conditions afforded *exo*-cycloadduct **17** in 88% yield. Breuer et al.[8] concluded that most cycloadditions between a nitrone and a monosubstituted ethylene

Table 1 1,3-Dipolar Cycloadditions of Spironitrone **5** with Dipolarophiles **11–15** To Give Cycloadducts **16–20**



Entry	1,3-Dipolarophile[a]	Cycloadduct	Yield (%)[b]
1	 **11**	 **16**	72 7:1 *exo*/*endo*
2	 **12**	 **17**	88 1.3:1 *exo*/*endo*
3	 **13**	 **18**	56
4	**14**	 **19**	55
5	**15**	 **20**	33

[a] Unless stated otherwise, cycloadditions were carried out using at least 3 equiv of dipolarophile.
[b] Isolated yields.

derivative lead to formation of 5-substituted isoxazolidines rather than the corresponding 4-isoxazolidines, regardless of the presence of electron-withdrawing or electron-donating groups. Surprisingly, however, heating spironitrone **5** in toluene under reflux with symmetrically substituted diene **13** (3 equiv) resulted in formation of a 1.3:1 mixture of C-15 epimers of cycloadduct **18** in 56% yield. The regiochemical outcome of the reaction was presumably dictated by steric effects in this case.[1]

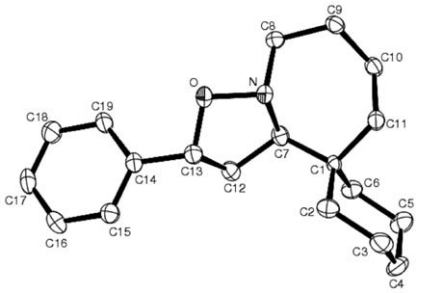


Figure 2 X-ray crystal structure of cycloadduct **16** (note different numbering system to that used in Table 1).

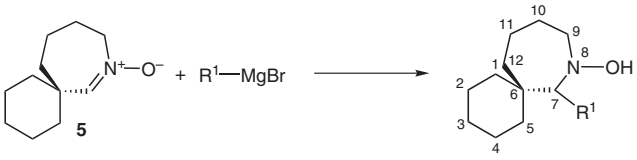
Individual reaction of spironitrone **5** with diphenylacetylene **14** (3 equiv) and phenylacetylene **15** (3 equiv) in toluene for 12 hours under reflux, afforded cycloadducts **19** and **20** in 55% and 33% yield respectively.

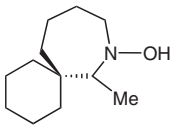
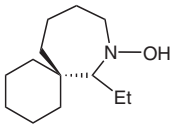
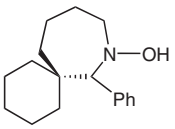
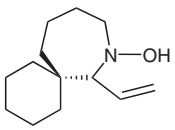
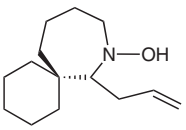
Addition of carbon nucleophiles to nitrones is a highly efficient method with which to prepare secondary hydroxylamines.[9] We therefore next focused on the reaction of several Grignard reagents with spironitrone **5** in order to generate a novel series of substituted spirocyclic hydroxylamines (Table 2).

In a typical procedure, spironitrone **5** was dissolved in tetrahydrofuran at 0 °C then treated with the organometallic reagent for one hour. Use of commercially available Grignard reagents (MeMgBr, EtMgBr, PhMgBr and CH_2=CHMgBr) afforded the corresponding hydroxylamines **21**, **22**, **23** and **24** in variable yields. Addition of allylmagnesium bromide to spironitrone **5** proved problematic, whilst addition of an allylzinc reagent did afford allyl substituted hydroxylamine **25** albeit in 30% yield. The latter proved to be highly sensitive, which may have contributed to the low yield of the product isolated from the reaction.

In conclusion, a concise synthesis of spironitrone **5** has been developed. Furthermore, the use of this spironitrone in 1,3-dipolar cycloadditions to a range of dipolarophiles has been demonstrated. Nucleophilic addition of several Grignard reagents to spironitrone **5** has facilitated access to a range of substituted spirocyclic secondary hydroxylamines. The heterocyclic motifs reported herein comprise the core 7,6-ring system of the spiroimine unit of the spirolide family of shellfish toxins, which is thought to be the key pharmacophore in these intrinsically bioactive molecules.

Table 2 Nucleophilic Addition of Organometallic Reagents to Spironitrone **5** to Give Hydroxylamines **21–25**



Entry	Reagent[a]	Hydroxylamine	Yield (%)[c]
1	MeMgBr	 **21**	86
2	EtMgBr	 **22**	72
3	PhMgBr	 **23**	38
4	CH_2=CHMgBr	 **24**	57
5	CH_2=CHCH$_2$ZnBr[b]	 **25**	30

[a] Unless stated otherwise, additions were carried out in THF at 0 °C for 1 h, using at least 3 equiv of organometallic reagent.
[b] THF, 0 °C to r.t., 0.5 h.
[c] Isolated yield.

All reactions were carried out under an N_2 atmosphere using oven-dried glassware and standard syringe and septum techniques, unless otherwise stated. THF was distilled from Na/benzophenone under N_2. CH_2Cl_2 was distilled from CaH_2 under N_2. Flash chromatography was performed using Riedel-de Häen or Merck 0.032–0.063 mm silica gel. Analytical TLC was performed with 0.20 mm silica gel 60 aluminium-backed plates and analysed using 365 nm ultraviolet irradiation, followed by staining with either alkaline permanganate or vanillin/H_2SO_4 solution. High-resolution mass spectra were obtained using EI, CI and FAB techniques on a VG70-SE spectrometer operating at a nominal accelerating voltage of 70 eV and a nominal resolution of 5000 to 10000 as appropriate. NMR spectra were recorded on either a Bruker DRX300 spectrometer operating at 300 MHz for ^{1}H nuclei and 75 MHz for ^{13}C nuclei or on a Bruker DRX400 spectrometer operating at 400 MHz for ^{1}H nuclei and 100 MHz for ^{13}C nuclei or on a Bruker DRX600 operating at 600 MHz for ^{1}H nuclei and 150 MHz for ^{13}C nuclei. ^{1}H NMR data is reported as chemical shift in δ ppm from TMS as an internal stan-

dard; multiplicity as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or overlap of non-equivalent resonances, br = broadening. ^{13}C NMR data is reported as follows: chemical shift in δ ppm from TMS with the solvent as an internal indicator ($CDCl_3$, δ = 77.0 ppm), multiplicity with respect to proton (deduced from DEPT experiments) is also reported.

Methyl 1-(4′-Bromobutyl)cyclohexanecarboxylate (7)

A solution of LDA was prepared by adding *n*-BuLi (1.6 M in hexane, 17.5 mL, 28.0 mmol) slowly over 30 min to a stirred suspension of diisopropylamine (4.35 mL, 30.8 mmol) in anhydrous THF (17 mL) at –78 °C under argon. After 30 min at –78 °C, methyl cyclohexanecarboxylate (**6**; 4.0 mL, 28 mmol) was added slowly to the stirring reaction mixture. After 30 min at –78 °C, 1,4-dibromobutane (10.3 mL, 84 mmol) was added slowly to the stirring reaction mixture. After 10 min at –78 °C, the reaction mixture was then allowed to warm to r.t. and the mixture was quenched with H_2O (15 mL), acidified with aq HCl (1 M, 10 mL) and extracted with Et_2O (3 × 10 mL). The combined extracts were dried over anhydrous $MgSO_4$, concentrated in vacuo and the residue was purified by flash chromatography (hexane–Et_2O, 19:1) to give the title compound **7**.

Yield: 6.25 g (88%); pale-yellow oil; R_f = 0.25 (hexane–Et_2O, 19:1).

IR (NaCl): 2937, 2854, 1728, 1452, 1432, 1222, 1209, 1160, 1136 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.13–1.70 (m, 4 H, 2 × CH_2), 1.33–1.55 (m, 8 H, 4 × CH_2), 1.75 (quin, *J* = 6.8 Hz, 2 H, H-3′), 2.01 (br d, *J* = 12.7 Hz, 2 H, CH_2), 3.32 (t, *J* = 6.7 Hz, 2 H, H-4′), 3.63 (s, 3 H, OCH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.6, 23.1, 25.8, 32.9, 33.2, 33.9, 34.1, 39.3 (all CH_2), 46.8 (q, C-1), 51.3 (CH_3, OCH_3), 176.9 (q, C=O).

MS (EI): *m*/*z* (%) = 276 (5) [M]$^+$, 217 (59), 142 (100), 93 (43), 70 (12).

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{12}H_{21}{}^{79}BrO_2$: 276.0725; found: 276.0721.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{12}H_{21}{}^{81}BrO_2$: 278.0704; found: 278.0706.

[1-(4′-Bromobutyl)cyclohexyl]methanol (8)

DIBAL-H (1.4 M in toluene, 12.5 mL, 17.4 mmol) was added slowly at –78 °C to a solution of methyl 1-(4′-bromobutyl)cyclohexanecarboxylate (**7**; 4.2 g, 15.3 mmol) in anhydrous toluene (50 mL) under argon. After 3 h at –78 °C, the reaction mixture was quenched with MeOH (40 mL), warmed to r.t. and filtered through a pad of Celite®. After removal of the solvents in vacuo, the residue was purified by flash chromatography (hexane–Et_2O, 2:1) to give the title compound **8**.

Yield: 3.0 g (80%); pale-yellow oil; R_f = 0.13 (hexane–Et_2O, 2:1).

IR (NaCl): 3376, 2827, 2859, 1453, 1264, 1242, 1037 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.24–1.30 (m, 4 H, 2 × CH_2), 1.33–1.50 (m, 10 H, 5 × CH_2), 1.83 (quin, *J* = 6.9 Hz, 2 H, H-3′), 3.41 (s, 2 H, H-1″), 3.42 (t, *J* = 6.7 Hz, 2 H, H-4′).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.4, 21.5, 26.3, 32.3, 33.4, 33.6 (all CH_2), 33.9 (CH_2 C-4′), 36.9 (q, C-1), 68.2 (CH_2, OCH_2).

MS (CI): *m*/*z* (%) = 266 (100) [M + NH_4]$^+$, 216 (50), 137 (129), 109 (20).

HRMS (CI): *m*/*z* [M + NH_4]$^+$ calcd for $C_{11}H_{25}{}^{79}BrNO$: 266.1119; found: 266.1121.

HRMS (CI): *m*/*z* [M + NH_4]$^+$ calcd for $C_{11}H_{25}{}^{81}BrNO$: 268.1099; found: 268.1100.

1-(4′-Bromobutyl)cyclohexanecarboxaldehyde (9)

PCC (15.8 g, 74.0 mmol) was added to a slurry of [1-(4′-bromobutyl)cyclohexyl]methanol (**8**; 6.13 g, 25.0 mmol) and Celite® (20 g) in anhydrous CH_2Cl_2 (100 mL). After 2 h at r.t., Et_2O (100 mL) was added and the mixture was filtered through a pad of Celite®. The filtrate was dried over anhydrous $MgSO_4$, concentrated in vacuo and the residue was purified by flash chromatography (hexane–EtOAc, 19:1) to give the title compound **9**.

Yield: 5.1 g (84%); pale-yellow oil; R_f = 0.30 (hexane–EtOAc, 19:1).

IR (NaCl): 2933, 2690, 1724, 1453, 1373, 1263, 1241, 1196, 1169, 953, 830, 744, 647 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.33–1.50 (m, 12 H, 6 × CH_2), 1.53–1.76 (m, 4 H, 2 × CH_2), 3.38 (t, *J* = 6.8 Hz, 2 H, H-4′), 9.40 (s, 1 H, CHO).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.6, 23.1, 25.7, 33.1, 33.2, 33.9, 34.6, 35.3 (all CH_2), 49.5 (q, C-1), 206.9 (CHO).

MS (EI): *m*/*z* (%) = 247 (2) [M]$^+$, 217 (32), 149 (100), 128 (90), 95 (40).

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{11}H_{18}{}^{79}BrO$: 245.0541; found: 245.0539.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{11}H_{18}{}^{81}BrO$: 247.0521; found: 247.0520.

1-(4′-Bromobutyl)cyclohexanecarbaldehyde Oxime (10)

A mixture of 1-(4′-bromobutyl)cyclohexanecarboxyaldehyde (**9**; 1.61 g, 6.50 mmol), hydroxylamine hydrochloride (450 mg, 6.50 mmol) and NaOAc (1.1 g, 13.4 mmol) in MeOH (20 mL) was stirred at r.t. overnight. The solvent was then removed in vacuo and the residue was quenched by the addition of sat. $NaHCO_3$ (10 mL). The mixture was extracted with EtOAc (3 × 10 mL) and the organic phase was washed with H_2O (10 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and the solvent was removed in vacuo. The resultant residue was purified by flash chromatography (hexane–EtOAc, 9:1) to give the title compound **10**.

Yield: 1.4 g (82%); colourless crystalline solid; mp 44.8–45 °C; R_f = 0.30 (hexane–EtOAc, 9:1).

IR (NaCl): 3325, 2931, 2853, 1738, 1449, 1299, 1242, 950, 930 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.25–1.66 (m, 12 H, 6 × CH_2), 1.69–1.74 (m, 2 H, CH_2), 1.76–1.85 (quin, *J* = 6.8 Hz, 2 H, H-3′), 3.38 (t, *J* = 6.7 Hz, 2 H, H-4′), 7.21 (s, 1 H, HC=N), 9.14 (s, 1 H, N-OH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.9, 22.0, 25.9, 33.1, 33.3, 34.1, 38.7 (all CH_2), 39.8 (q, C-1), 157.4 (CH_2, C-1″).

MS (EI): *m*/*z* (%) = 261 (5) [M]$^+$, 183 (100), 81 (60), 73 (45).

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{11}H_{20}{}^{79}BrNO$: 261.0728; found: 261.0726.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{11}H_{20}{}^{81}BrNO$: 263.0707; found: 263.0721.

8-Azoniaspiro[5.6]dodec-7-en-8-olate (5)

A mixture of 1-(4′-bromobutyl)cyclohexanecarbaldehyde oxime (**10**; 50.0 mg, 0.19 mmol) and K_2CO_3 (80 mg, 0.57 mmol) in acetone–H_2O (4:1, 3 mL) was put in a microwave reactor at 110 W, 90 °C, 100 psi for 4 h. The mixture was cooled to r.t., diluted with H_2O (3 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined extracts were dried over anhydrous $MgSO_4$ and the solvent was removed in vacuo. The residue was purified by flash chromatography (CH_2Cl_2–MeOH, 19:1) to give the title compound **5**.

Yield: 16 mg (46%); unstable colourless oil; R_f = 0.13 (CH_2Cl_2–MeOH, 19:1).

IR (NaCl): 2930, 2854, 2210, 1580, 1448, 1242, 1179, 1150, 1104, 924, 909 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 1.27–1.31 (m, 3 H, H_a-1, H_a-3 and H_a-5), 1.37–1.42 (m, 2 H, H-4), 1.52–1.58 (m, 5 H, 2 × CH_2 and H_b-3), 1.74–1.85 (m, 6 H, 2 × CH_2, H_b-1 and H_b-5), 4.12 (m, 2 H, H-9), 7.04 (s, 1 H, H-7).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 21.8, 22.7, 25.3, 25.6, 35.6, 36.5 (all CH_2), 37.5 (q, C-6), 64.8 (CH_2, C-9), 146.0 (CH, HC=N).

MS (EI): *m*/*z* (%) = 181 (99) $[M]^+$, 122 (59), 84 (100).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{11}H_{19}NO$: 181.1466; found: 181.1464.

8-Aza-14-phenylisoxazolo[2,3-*g*]spiro[5.6]dodecane (16)

Spironitrone **5** (550 mg, 1.96 mmol) and styrene (905 μL, 7.9 mmol) were dissolved in toluene (10 mL) under an argon atmosphere and the solution was heated under reflux for 12 h. After cooling to r.t., the reaction mixture was concentrated in vacuo and the residue was purified by flash chromatography (hexane–EtOAc, 10:1) to give an inseparable mixture (7:1) of the title compound **16** and the C-14 epimer. Recrystallization from Et_2O gave white prisms, which were subjected to single crystal X-ray analysis, confirming the structure of the major component. Chemical shifts for the minor C-14 epimer are indicated by an asterisk (*).

Yield: 403 mg (72%); white solid.

IR (NaCl): 3031, 2927, 2861, 2246, 1947, 1874, 1806, 1738, 1605, 1496, 1452, 1371, 1243, 1048 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.02–1.15 (m, 2 H, CH_2), 1.17–1.25 (m, 1 H, CH_a), 1.27–1.85 (m, 12 H, 6 × CH_2), 1.95 (dd, *J* = 12.9, 8.1 Hz, 1 H, CH_b), 2.22 (dt, *J* = 12.4, 10.4 Hz, 1 H, H_a-15), 2.32* (q, *J* = 11.1 Hz, 1 H, H_a-15), 2.41–2.47* (m, 1 H, H_b-15), 2.52–2.58 (m, 1 H, H_b-15), 2.72 (dt, *J* = 11.5, 4.4 Hz, 1 H, H_a-9), 2.84 (dd, *J* = 10.6, 4.0 Hz, 1 H, H-7), 2.95–3.06* (m, 1 H, H_a-9), 3.47–3.53* (m, 1 H, H_b-9), 3.54–3.62 (m, 1 H, H_b-9), 4.79 (dd, *J* = 10.0, 5.8 Hz, 1 H, H-14), 5.19* (dd, *J* = 10.5, 4.4 Hz, 1 H, H-14), 7.25–7.35 (m, 3 H, ArH), 7.37–7.39 (m, 2 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.7, 20.9, 21.0*, 21.5, 21.6*, 26.4, 28.0*, 31.3*, 31.5, 33.5, 34.3*, 34.4 (all CH_2), 36.3 (q, C-6), 39.4 (CH_2, C-15), 41.6* (CH_2, C-15), 59.5 (CH_2, C-9), 60.2* (CH_2, C-9), 76.8 (CH, C-7), 77.8* (CH, C-7), 78.2 (CH, C-14), 78.3* (CH, C-14), 126.3* (CH, ArH), 126.7 (CH, ArH), 127.7* (CH, ArH), 127.8 (CH, ArH), 128.2* (CH, ArH), 128.3 (CH, ArH), 139.1 (q, Ar).

MS (EI): *m*/*z* (%) = 285 (32) $[M]^+$, 69 (100).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{19}H_{27}NO$: 285.2092; found: 285.2091.

8-Aza-14-[1′-benzyl-*N*-methylcarbamate]isoxazolo[2,3-*g*]spiro[5.6]dodecane (17)

Spironitrone **5** (50.0 mg, 276 μmol) and benzyl *N*-allylcarbamate (158 mg, 828 μmol) was dissolved in toluene (10 mL) under an argon atmosphere and the solution was heated under reflux for 12 h. The reaction mixture was cooled to r.t. and the solvent was concentrated in vacuo. The residue was purified by flash chromatography (hexane–Et_2O, 2:1) to give the title compound **17**.

Yield: 90 mg (88%); colourless oil.

IR (NaCl): 2929, 2862, 2248, 1717, 1517, 1453, 1251, 909 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.93–1.13 (m, 2 H, CH_2), 1.16–1.79 (m, 13 H, 6 × CH_2 and CH_a), 1.82–1.93 (m, 2 H, CH_2), 2.17–2.26 (m, 1 H, CH_b), 2.58 (dt, *J* = 11.1, 4.7 Hz, 1 H, H_a-9), 2.66 (dd, *J* = 10.3, 4.7 Hz, 1 H, H-14), 3.16–3.25 (m, 1 H, H_a-1′), 3.40–3.45 (m, 1 H, H_b-9), 3.54 (m, 1 H, H_b-1′), 3.88–3.96 (m, 1 H, H-7), 5.05 (br s, 1 H, NH), 5.09 (s, 2 H, OCH_2), 7.26–7.38 (m, 5 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.7, 20.9, 21.5, 26.4, 27.8, 31.3, 33.6, 34.2, 34.3 (all CH_2), 36.1 (q, C-6), 42.9 (CH_2, C-1′), 59.3 (CH_2, C-9), 66.7 (CH_2, CBz), 75.4 (CH, C-7), 76.5 (CH, C-14), 128.0 (CH, ArH), 128.0 (CH, ArH), 128.5 (CH, ArH), 136.5 (q, Ar), 156.5 (q, C=O).

MS (EI): *m*/*z* (%) = 372 (18) $[M]^+$.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{22}H_{32}N_2O_3$: 372.2412; found: 372.2409.

8-Aza-15-[1′-(2′,2′-diethyloxycarbonylpent-4′-enyl)]isoxazolo[2,3-*g*]spiro[5.6]dodecane (18)

Spironitrone **5** (143 mg, 790 μmol) and diethyl 2,2-diallylmalonate (564 mg, 2.37 mmol) was dissolved in toluene (10 mL) under an argon atmosphere and the solution was heated under reflux for 12 h. The reaction mixture was cooled to r.t., the solvent was concentrated in vacuo and the residue was purified by flash chromatography (hexane–EtOAc, 5:1) to give an inseparable mixture (1.3:1) of the title compound **18** and the C-15 epimer. Chemical shifts for the C-15 epimer are indicated by an asterisk (*).

Yield: 186 mg (56%); yellow oil.

IR (NaCl): 2980, 2930, 2862, 1733, 1463, 1446, 1286, 1218, 1198, 1143, 1097 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.20–1.24 (2 × t, *J* = 7.4 Hz, 6 H, 2 × OCH_2CH_3), 1.16–1.91 (m, 16 H, 8 × CH_2), 2.13–2.25 (m, 2 H, CH_2), 2.17–2.19 (m, 2 H, CH_2), 2.50–2.65 (m, 1 H, H_a-9), 2.64–2.81 (m, 1 H, H-7), 3.37–3.42 (m, 1 H, H_b-9), 3.73–3.81 (m, 1 H, H-15), 4.10–4.19 (m, 2 H, H-14), 4.17* (q, *J* = 7.1 Hz, 2 H, OCH_2CH_3), 4.18 (q, *J* = 7.1 Hz, 2 H, OCH_2CH_3), 5.07 (br d, *J* = 9.9 Hz, 1 H, H_a-5′), 5.12 (m, 1 H, H_b-5′), 5.70 (m, 1 H, H-4′).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0 (CH_3, OCH_2CH_3), 14.07* (CH_3, OCH_2CH_3), 14.1 (CH_3, OCH_2CH_3), 20.7, 20.9, 21.6, 22.1, 26.4, 28.1, 31.3, 33.5, 34.4 (all CH_2), 36.0 (q, C-6), 36.1, 36.7, 36.8* (all CH_2), 56.2, 57.2 (q, C-2′), 59.6 (CH_2, C-9), 61.2 (CH_2, OCH_2CH_3), 61.3 (CH_2, C-14), 72.4 (CH, C-15), 76.1 (CH, C-7), 119.0* (CH_2, C-5′), 119.1 (CH_2, C-5′), 132.3 (CH, C-4′), 132.7* (CH, C-4′), 170.7 (q, C=O), 171.0 (q, C=O).

MS (EI): *m*/*z* (%) = 421 (42) $[M]^+$, 69 (100).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{24}H_{39}NO_5$: 421.2828; found: 421.2832.

8-Aza-14,15-diphenylisoxazolino[2,3-*g*]spiro[5.6]dodecane (19)

Spironitrone **5** (50 mg, 276 μmol) and diphenylacetylene (147 mg, 828 μmol) were dissolved in toluene (10 mL) under an argon atmosphere and the mixture was heated under reflux for 12 h. The reaction mixture was cooled to r.t. and the solvent was concentrated in vacuo. The residue was purified by preparative layer chromatography (hexane) on a 20 cm × 20 cm plate to give the title compound **19**.

Yield: 54 mg (55%); pale-yellow oil.

IR (NaCl): 3056, 3025, 2925, 2858, 2247, 1949, 1884, 1806, 1661, 1601, 1497, 1446, 1245, 1129 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.78–0.95 (m, 1 H, CH_a), 0.98–1.12 (m, 1 H, CH_b), 1.16–1.53 (m, 8 H, 4 × CH_2), 1.54–1.65 (m, 2 H, CH_2), 1.69–1.84 (m, 3 H, CH_2 and CH_a), 2.08 (dd, *J* = 13.8, 8.3 Hz, 1 H, CH_b), 3.06 (dt, *J* = 10.9, 5.4 Hz, 1 H, H_a-9), 3.72–3.78 (m, 1 H, m, H_b-9), 4.46 (s, 1 H, 7-H), 7.10–7.18 (m, 5 H, ArH), 7.20–7.33 (m, 5 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.0, 21.2, 21.8, 26.1, 28.7, 30.7, 33.9, 34.4 (all CH_2), 38.7 (q, C-6), 61.7 (CH_2, C-9), 86.4 (CH, C-7), 108.0 (q, C-15), 126.7, 127.4 (CH, ArH), 127.8 (CH, ArH), 128.2

(CH, ArH), 128.5 (CH, ArH), 129.2 (q, Ar), 130.3 (CH, ArH), 135 (q, Ar), 146.7 (q, C-14).

MS (EI): *m/z* (%) = 359 (55) $[M]^+$, 105 (100).

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{25}H_{29}NO$: 359.2249; found: 359.2239.

8-Aza-14-phenylisoxazolino[2,3-*g*]spiro[5.6]dodecane (20)

Spironitrone **5** (50 mg, 276 μmol) and ethynylbenzene (90 μL, 828 μmol) were dissolved in toluene (10 mL) under an argon atmosphere and the mixture was heated under reflux for 12 h. The reaction mixture was cooled to r.t. and the solvent was concentrated in vacuo. The residue was purified by preparative layer chromatography (hexane–EtOAc, 20:1) on a 20 × 20 cm plate to give the title compound **20**.

Yield: 26 mg (33%); pale-yellow oil.

IR (NaCl): 2925, 2857, 1947, 1879, 1804, 1726, 1655, 1494, 1448, 1326, 1280, 1061 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.05–1.22 (m, 2 H, CH_2), 1.23–1.84 (m, 13 H, 6 × CH_2), 2.01 (dd, *J* = 13.1, 8.0 Hz, 1 H, CH_b), 3.00 (dt, *J* = 10.9, 4.8 Hz, 1 H, H_a-9), 3.75–3.80 (m, 1 H, H_b-9), 4.02 (d, *J* = 2.0 Hz, 1 H, H-7), 5.14 (d, *J* = 2.1 Hz, 1 H, H-15), 7.25–7.35 (m, 3 H, ArH), 7.49–7.54 (m, 2 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.1, 21.2, 21.8, 26.5, 28.6, 32.9, 34.5, 34.7 (all CH_2), 36.7 (q, C-6), 61.0 (CH_2, C-9), 83.8 (CH, C-7), 93.5 (CH, C-15), 125.2 (CH, ArH), 128.2 (CH, ArH), 128.4 (CH, ArH), 151.4 (q, Ar).

MS (FAB): *m/z* (%) = 284 (100) $[M + H]^+$.

HRMS (FAB): *m/z* $[M + H]^+$ calcd for $C_{19}H_{26}NO$: 284.2014; found: 284.2012.

7-Methyl-8-azaspiro[5.6]dodecan-8-ol (21)

A solution of MeMgBr (3.0 M in Et_2O, 193 μL, 579 μmol) was added dropwise to a solution of spironitrone **5** (30.0 mg, 165 μmol) in anhydrous THF (5 mL) at 0 °C under an argon atmosphere. The mixture was stirred for 1 h at 0 °C then quenched with sat NH_4Cl (10 mL). The mixture was extracted with Et_2O (3 × 15 mL) and the organic phase was washed with H_2O (2 × 10 mL) and brine (2 × 10 mL). The combined extracts were dried over anhydrous $MgSO_4$, concentrated in vacuo and the residue was purified by flash chromatography (hexane–Et_2O, 2:1) to give the title compound **21**.

Yield: 28 mg (86%); colourless oil.

IR (NaCl): 3232, 2927, 2855, 1597, 1449, 1373, 1150, 909, 733 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.09 (d, *J* = 6.8 Hz, 3 H, H-1′), 1.15–1.70 (m, 15 H, H_a-10 and 7 × CH_2), 1.74–1.87 (m, 1 H, H_b-10), 2.99–3.15 (m, 2 H, H-9), 3.23 (q, *J* = 6.8 Hz, 1 H, H-7), 7.81 (br s, 1 H, N-OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 7.2 (CH_3, C-1′), 20.4, 21.7, 25.5, 26.3, 34.2, 34.5, 36.8 (all CH_2), 37.7 (q, C-6), 54.2 (CH_2, C-9), 69.8 (CH, C-7).

MS (EI): *m/z* (%) = 197 (16) $[M]^+$, 180 (100) $[M - OH]^+$.

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{12}H_{23}NO$: 197.1779; found: 197.1779.

7-Ethyl-8-azaspiro[5.6]dodecan-8-ol (22)

A solution of EtMgBr (3.0 M in Et_2O, 383 μL, 1.10 mmol) was added dropwise to a solution of spironitrone **5** (70.0 mg, 386 μmol) in anhydrous THF (5 mL) at 0 °C under an argon atmosphere. The mixture is stirred for 1 h at 0 °C then quenched with sat. NH_4Cl (10 mL). The mixture was extracted with Et_2O (3 × 15 mL) and the organic phase was washed with H_2O (2 × 10 mL) and brine (2 × 10 mL). The combined extracts were dried over anhydrous $MgSO_4$, concentrated in vacuo and the residue was purified by flash chromatography (hexane–Et_2O, 4:1) to give the title compound **22**.

Yield: 59 mg (72%); pale-yellow oil.

IR (NaCl): 3216, 2929, 2857, 2221, 1597, 1461, 1149, 1124 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.03 (t, *J* = 7.4 Hz, 3 H, H-2′), 1.27–1.77 (m, 18 H, 9 × CH_2), 2.62–2.67 (m, 1 H, H-7), 2.91–2.98 (m, 1 H, H_a-9), 3.21–3.27 (dt, *J* = 10.3, 5.1 Hz, 1 H, H_b-9), 7.09 (br s, 1 H, N-OH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.9 (CH_3, C-2′), 18.3 (CH_2, C-1′), 21.5, 22.1, 22.2, 26.4, 26.8, 34.1, 34.4, 36.4 (all CH_2), 39.8 (q, C-6), 57.2 (CH_2, C-9), 77.6 (CH, C-7).

MS (EI): *m/z* (%) = 211 (3) $[M]^+$, 41 (100).

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{13}H_{25}NO$: 211.1936; found: 211.1938.

7-Phenyl-8-azaspiro[5.6]dodecan-8-ol (23)

A solution of PhMgBr (3.0 M in Et_2O, 167 μL, 502 mol) was added dropwise to a solution of spironitrone **5** (26 mg, 143 μmol) in anhydrous THF (5 mL) at 0 °C under an argon atmosphere. The mixture was stirred for 1 h at 0 °C then quenched with sat. NH_4Cl (10 mL). The mixture was extracted with Et_2O (3 × 15 mL) and the organic phase washed with H_2O (2 × 10 mL) and brine (2 × 10 mL). The combined extracts were dried over anhydrous $MgSO_4$, concentrated in vacuo and the residue was purified by flash chromatography (hexane–Et_2O, 4:1) to give the title compound **23**.

Yield: 14 mg (38%); colourless oil.

IR (NaCl): 2936, 2863, 1793, 1731, 1600, 1466, 1377, 1251, 1096 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.82–0.89 (m, 1 H, CH_a), 0.97 (dt, *J* = 12.7, 4.7 Hz, 1 H, CH_b), 1.18–1.32 (m, 4 H, 2 × CH_2), 1.32–1.52 (m, 4 H, 2 × CH_2), 1.53–1.67 (m, 4 H, 2 × CH_2), 1.80–2.04 (m, 2 H, CH_2), 3.12–3.23 (m, 1 H, H_a-9), 3.34 (ddd, *J* = 13.3, 6.9, 3.0 Hz, 1 H, H_b-9), 3.52 (s, 1 H, H-7), 4.64 (s, 1 H, N-OH), 7.23–7.35 (m, 5 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.8, 21.6, 21.8, 23.7, 25.7, 30.2, 31.9, 36.4 (all CH_2), 38.5 (q, C-6), 58.1 (CH_2, C-9), 85.5 (CH, C-7), 126.7 (CH, ArH), 127.6 (CH, ArH), 129.8 (CH, ArH), 141.6 (q, Ar).

MS (EI): *m/z* (%) = 259 (6) $[M]^+$, 242 (100) $[M - OH]^+$.

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{17}H_{25}NO$: 259.1936; found: 259.1932.

7-Vinyl-8-azaspiro[5.6]dodecan-8-ol (24)

A solution of vinylmagnesium bromide (1.0 M in THF, 828 μL, 828 μmol) was added dropwise to a solution of spironitrone **5** (50.0 mg, 276 μmol) in anhydrous THF (5 mL) at 0 °C under an argon atmosphere. The mixture was stirred for 1 h at 0 °C then quenched with sat. NH_4Cl (10 mL). The mixture was extracted with Et_2O (3 × 15 mL) and the organic phase washed with H_2O (2 × 10 mL) and brine (2 × 10 mL). The combined extracts were dried over anhydrous $MgSO_4$, concentrated in vacuo and the residue was purified by flash chromatography (hexane–EtOAc, 4:1) to give the title compound **24**.

Yield: 33 mg (57%); colourless oil.

IR (NaCl): 3232, 2927, 2858, 1738, 1595, 1455, 1240, 1106 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.13–1.69 (m, 14 H, 7 × CH_2), 1.72–1.93 (m, 2 H, CH_2), 2.86–2.96 (m, 1 H, H_a-9), 3.05–3.18 (m, 1 H, H_b-9), 3.49 (d, *J* = 9.8 Hz, 1 H, H-7), 4.96 (br s, 1 H, N-OH), 5.27 (dd, *J* = 16.4, 1.4 Hz, 1 H, H_a-2′), 5.39 (dd, *J* = 10.2, 2.1 Hz, 1 H, H_b-2′), 5.91 (dt, *J* = 16.8, 6.5 Hz, 1 H, H-1′).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.4, 21.4, 21.5, 25.6, 26.3, 34.1, 36.6, 36.7 (all CH_2), 36.9 (q, C-6), 55.6 (CH_2, C-9), 78.5 (CH, C-7), 121.3 (CH_2, C-2′), 132.2 (CH, C-1′).

MS (FAB): *m*/*z* (%) = 211 (52) $[M - H]^+$, 192 (17), 164 (45).

HRMS (FAB): *m*/*z* $[M - H]^+$ calcd for $C_{13}H_{22}NO$: 208.1701; found: 208.1693.

7-Allyl-8-azaspiro[5.6]dodecan-8-ol (25)

A solution of allylzinc bromide (0.6 M in THF, 2.2 mL, 1.3 mmol) was added dropwise to a solution of spironitrone **5** (80 mg, 441 μmol) in anhydrous THF (5 mL) at 0 °C under an argon atmosphere. The mixture was stirred for 30 min at r.t. then quenched with sat. $NaHCO_3$ (10 mL). The mixture was filtered through a pad of Celite®, extracted with Et_2O (3 × 15 mL), and the organic phase was washed with H_2O (2 × 10 mL) and brine (2 × 10 mL). The combined extracts were dried over anhydrous Na_2SO_4, concentrated in vacuo and the residue was purified by flash chromatography (hexane–Et_2O, 3:1) to give the title compound **25**.

Yield: 30 mg (30%); colourless oil.

IR (NaCl): 3233, 2927, 2858, 1740, 1637, 1452, 1241, 1047 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.25–1.80 (m, 17 H, N-OH, 8 × C*H*$_2$), 2.20–2.26 (m, 1 H, H_a-1′), 2.49–2.56 (m, 1 H, H_b-1′), 3.00–3.07 (m, 2 H, m, H_a-9 and H-7), 3.21–3.27 (m, 1 H, H_a-9), 4.97–5.01 (m, 1 H, H_a-3′), 5.07 (ddd, *J* = 17.0, 3.2, 1.5 Hz, 1 H, H_b-3′), 5.97–6.07 (m, 1 H, H-2′).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.9, 21.6, 21.7, 24.9, 26.3, 30.4, 34.1, 34.7, 36.4 (all CH_2), 39.3 (q, C-6), 56.1 (CH_2, C-9), 74.4 (CH, C-7), 114.6 (CH_2, C-3′), 140.3 (CH, C-2′).

MS (CI): *m*/*z* (%) = 221 (61) $[M + H]^+$, 220 (100), 206 (68), 98 (69).

HRMS (CI): *m*/*z* $[M - H]^+$ calcd for $C_{14}H_{24}NO$: 222.1858; found: 222.1853.

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