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X=Y–ZH compounds as potential 1,3-dipoles. Part 63: Silver catalysed azomethine ylide cycloaddition—the synthesis of spiro homoserine lactone analogues

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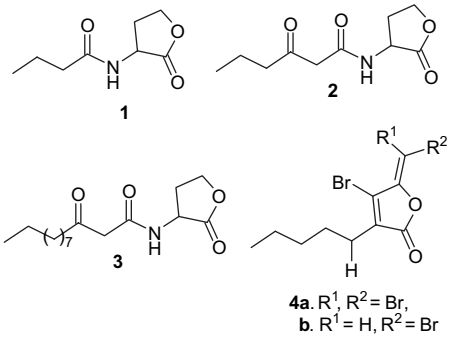
Abstract—A range of room temperature 1,3-dipolar cycloaddition reactions of imines of 2-amino-γ-lactone and thiolactone, catalysed by a combination of AgOAc or Ag_2O with NEt_3 or DBU, are described. The spiro lactones/thiolactones are formed regio- and stereoselectively as single cycloadducts in good yield via the *syn* dipoles and an *endo*-transition states.

1. Introduction

Homoserine lactone derivatives have attract much attention due to their biological activity profile.[1] Acyl homoserine lactones (AHLs) **1**–**3** are important intercellular signalling molecules in many Gram-negative bacteria and are responsible for bacterial quorum sensing.[2] Both antagonist and agonist AHLs have been reported for Gram-negative bacteria.[3] The seaweed *Delisea pulchra* produces a number of halogenated furanones **4a**,**b**, structurally similar to the bacterial AHLs, which exhibit antifouling and antimicrobial properties.[4] Synthetic analogues of AHLs possess inhibitory and immune modulatory activity in both eukaryotic and prokaryotic cells.[5]

Spiropyrrolidines have attracted attention because of their antiviral[6] and local anaesthetic[7] activity and as potential anitleukemic and anticonvulsant agents.[8] Recently, several reports[9–12] have appeared of the synthesis of substituted spiropyrrolidines using azomethine ylide cycloaddition reactions. Raghunathan et al. reported the synthesis and biological activity of new classes of spiro- and bis-spiropyrrolidines.[11] The spiropyrrolidine ring system also occurs in alkaloids,[12] for example, (−)-horsfiline[12a] and spirotryprostatin A,[12b] which have been synthesised using azomethine ylide cycloaddition reactions. A few reports describing the use of methylene lactones as dipolarophiles in azomethine ylide cycloaddition reactions generating spiropyrrolidines have appeared.[13]



Our group has developed a wide variety of protocols for the synthesis of polysubstituted pyrrolidines involving imine substrates.[14–16] Appropriate imines generate azomethine ylides in situ via thermal 1,2-prototropy or Bronsted acid catalysis[14] or by decarboxylative processes.[15] Alternatively metallo-azomethine ylides can be generated catalytically at room temperature by combination of a metal salt and a tertiary amine.[16] In this context, imines of homoserine lactone **5** and homocysteine thiolactone **6** offer access to spiro analogues. This paper describes application of the catalytic metallo-azomethine ylide process to the synthesis of diverse analogues of **5** and **6** via silver salt catalysis.

A variety of aldehydes (aryl, heteroaryl or aliphatic) were employed to illustrate the diversity of the metallo-azomethine ylide cycloaddition (Scheme 1). In some cases long-chain aliphatic aldehydes were used to increase the lipophilicity of the cycloadducts. A series of aryl/heteroaryl

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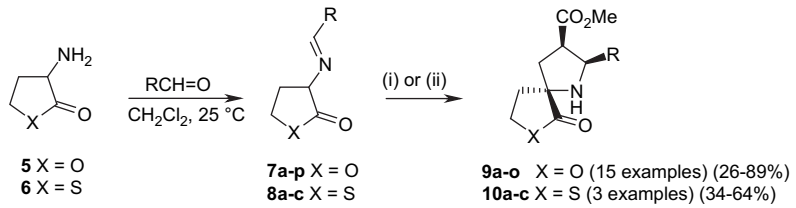
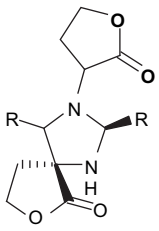


Scheme 1. Reagents and conditions: (i) NEt_3, AgOAc in MeCN, 25 °C; (ii) NEt_3 or DBU, AgO in toluene, 25 °C.

7b–d and aliphatic **7e–o** imines of α-amino-γ-butyrolactone **5** were prepared in good yield (85–99%) by condensation of **5** with the appropriate aldehydes in the presence of a dehydrating agent ($MgSO_4$) in a suitable solvent at room temperature (Table 1, entries 1–15). Imine **7a** (R=Ph) was obtained using a literature method.[17] Attempts to prepare imines of **5** with 2- and 4-pyridine carboxaldehyde and *N*-methyl imidazole-2-carboxaldehyde resulted in complex reaction mixtures. Imines **8a–c** were obtained at room temperature in 86–95% yield by the analogous condensation of **6** with the appropriate aldehyde (Table 1, entries 16–18).

The aryl/heteroaryl imines **7a–d** reacted regio- and stereospecifically with methyl acrylate (1.2 equiv) in acetonitrile at room temperature in the presence of AgOAc (1.5 equiv) and NEt_3 (1.1 equiv) to give single cycloadducts **9a–d** in 48–86% yield (Table 1, entries 1–4). The low yield of cycloadduct **9b** probably arises from the formation of some imine dimer product **11** due to the high reactivity of the 3-pyridyl imine.[18] The reactions were completed in 3–4 h in the case of imines **7a**,**b**,**d** whilst **7c** required 24 h. This longer reaction time appears to be due to the poor solubility of the imine in acetonitrile.



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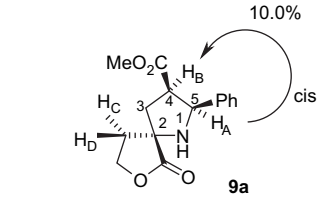
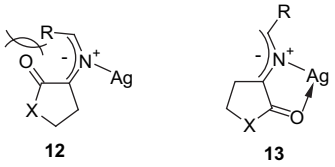
In contrast to aryl imines, cycloaddition of aliphatic aldimines **7e–o** was carried out in toluene. Previous experiments[19] suggested that the Ag(I) catalysed cycloaddition reactions of alanine ester imines of aliphatic aldehydes in acetonitrile resulted in the formation of an additional (minor) cycloadduct arising from the *E*,*Z*-metallo-dipole **12**. However, it has also been reported that a mixture of *syn*-endo and *anti*-endo cycloadducts were obtained in both acetonitrile and toluene.[20]

The recent introduction[21] of a catalytic method using Ag_2O (10 mol %) for the generation of metallo-azomethine ylide is very effective in the case of imines **7e–o.** The latter were subjected to 1,3-dipolar cycloaddition reactions with methyl acrylate in toluene in the presence of NEt_3 and Ag_2O (10 mol %) at room temperature (Table 1, entries 5–15). The cycloaddition of imines **7e**,**m** afforded single cycloadducts **9e**,**m** (Table 1, entries 5 and 13) in good yield (86–89%), whereas racemic aldimines **7f**,**h–l**,**o** afforded diastereomeric mixtures (dr; 1:1 to 1:3) of cycloadducts **9f**,**h–l**,**o** (Table 1, entries 6, 8–12 and 15) (due to the chiral centre present in the aldimine substituent). In the case of **9l**,**o** it was possible to separate both diastereomers using silica gel chromatography but it did not prove possible to achieve a similar separation for **9h–k** (see Section 2). The chiral aldimines **7g**,**n** afforded 1:1 mixtures of chiral diastereomers **9g**,**n** (Table 1, entries 7 and 14). The diastereomers of **9n** were separated by silica gel chromatography, whereas those of **9g** were inseparable. The low yield of **9g** appears to be due to competitive metal catalysed hydrolysis of the imine as evidenced by the isolation of the hydrolysis products and the ^1H NMR spectrum of the crude reaction mixture which showed it to comprise a 1:1 mixture of cycloadducts and hydrolysis products.



9a

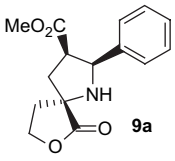
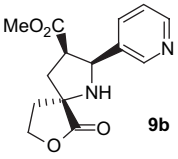
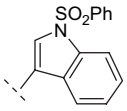
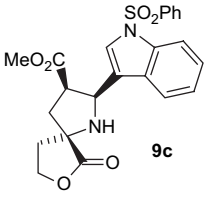
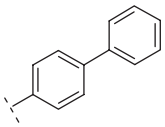
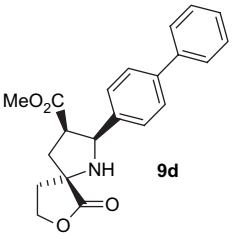
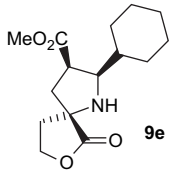
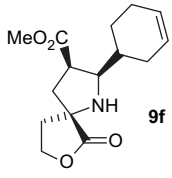
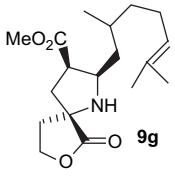
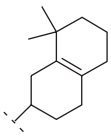
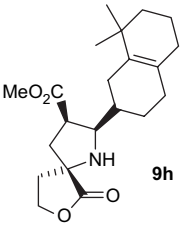


12 **13**

Racemic imines **8a–c** underwent cycloaddition with methyl acrylate in the presence of DBU as base to afford mixture of diastereomeric cycloadducts **10a–c** in 34–64% yield (Table 1, entries 16–18). Previously, we reported[19] related cycloadditions of aliphatic aldimines using NEt_3 as base. However, in the case of **8a–c** NEt_3 was ineffective. Imines **8a**,**b** gave a 1:1 mixture of diastereomers **10a**,**b** (inseparable), whereas **8c** gave a 3:1 mixture of separable diastereomers of **10c**. The cycloadditions of **8a–c** were regio- and *endo*-selective.

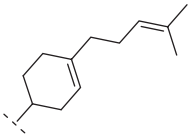
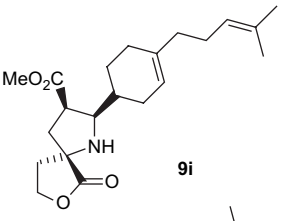
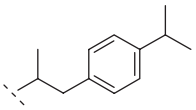
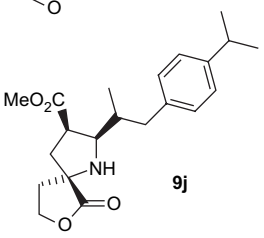
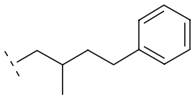
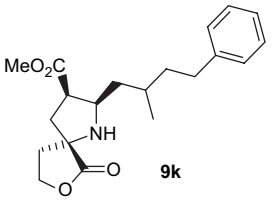
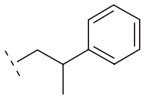
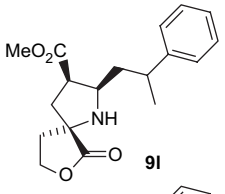
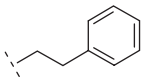
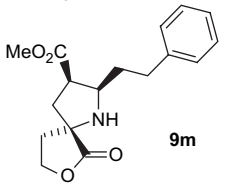
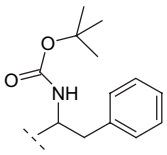
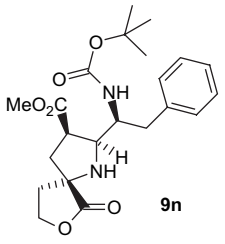
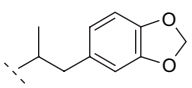
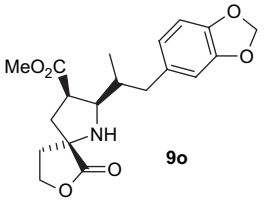
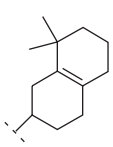
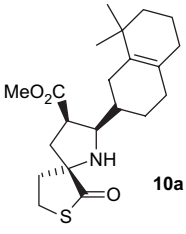
In all cases, the imines **7a–o** and **8a–c** generate the corresponding metallo-1,3-dipoles **13** stereoselectively, based on cycloadduct stereochemistry, and the dipole configuration is analogous to that obtained from imines of α-amino esters.[22] In these cases, the dipoles are formed under kinetic control and the co-ordination of the metal depicted in **13** together with steric effects arising from interaction of R and the carbonyl group in **12** are believed to be responsible for this kinetic preference. The cycloadducts arise from **13** via *endo*-transition states. The relative stereochemistry of the cycloadducts was determined by NOE studies. For example, the irradiation of H_A in **9a** effects a 10% enhancement of the signal for H_B indicating a cis relationship between them.

Table 1. Silver salt/base catalysed cycloaddition of **7a–o** and **8a–c** with methyl acrylate[a–c]

Entry	Imine	R	Cycloadduct	Yield (%)[d]
1[a]	**7a**		 **9a**	86
2[a]	**7b**		 **9b**	48
3[a]	**7c**		 **9c**	54
4[a]	**7d**		 **9d**	57
5[b]	**7e**		 **9e**	89
6[b]	**7f**		 **9f**	57[e]
7[b]	**7g**		 **9g**	26[e]
8[b]	**7h**		 **9h**	52[e]

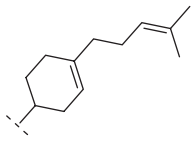
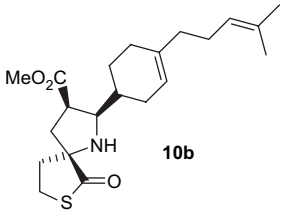
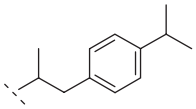
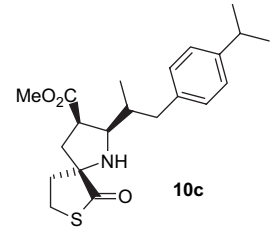
(*continued*)

Table 1. (*continued*)

Entry	Imine	R	Cycloadduct	Yield (%)[d]
9[b]	**7i**		 **9i**	81[e]
10[b]	**7j**		 **9j**	72[f]
11[b]	**7k**		 **9k**	68[e]
12[b]	**7l**		 **9l**	71[e]
13[b]	**7m**		 **9m**	86
14[b]	**7n**		 **9n**	46[e]
15[b]	**7o**		 **9o**	80[f]
16[c]	**8a**		 **10a**	34[e]

(*continued*)

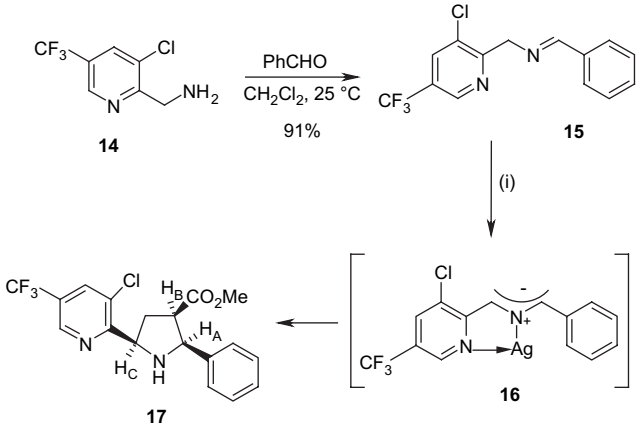
Table 1. (*continued*)

Entry	Imine	R	Cycloadduct	Yield (%)[d]
17[c]	**8b**		 **10b**	64[e]
18[c]	**8c**		 **10c**	64[f]

[a] Entries 1–4: acetonitrile, NEt_3 (1.1 equiv), AgOAc (1.5 equiv), 25 °C.
[b] Entries 5–15: toluene, NEt_3 (1.1 equiv), Ag_2O (10 mol %), 25 °C.
[c] Entries 16–18: toluene, DBU (1 equiv), Ag_2O (10 mol %), 25 °C.
[d] Isolated yield.
[e] 1:1 Mixture of diastereomers.
[f] 1:3 Mixture of diastereomers.

The regiochemistry of the cycloadducts was assigned by comparing the coupling pattern of the relevant protons in the ^{1}H NMR spectra. In the spectra of the cycloadducts, H_A appears as a dd (due to coupling with H_B and NH protons) whilst H_B appears either as a ddd or dt due to coupling with H_A and the C(3)–CH_2 group.

Trifluoromethylated pyridines are widely applied in the field of medicinal and agricultural chemistry.[23] Imine **15**, derived from trifluoromethyl pyridine **14**, underwent regio- and stereo-specific 1,3-dipolar cycloaddition with methyl acrylate in toluene in the presence of Ag_2O (10 mol %) and NEt_3 to give a single cycloadduct **17** in 44% yield (Scheme 2). Cycloadduct **17** arises from dipole **16** via an *endo*-transition state. Thermal 1,2-prototropy-cycloaddition gave a mixture of *endo* -and *exo*-cycloadduct for similar reactions.[24] The dipole **16** is formed under kinetic control and the coordination of the metal depicted in **16** is believed to be responsible for this kinetic preference.



Scheme 2. Reagents and conditions: (i) Methyl acrylate, NEt_3, Ag_2O, toluene, 5 h at 25 °C.

The relative stereochemistry of **17** was assigned by NOE studies (see Section 2). The irradiation of H_A effects a 9% enhancement of the signal for H_B and a 2% enhancement for H_C, whilst irradiation of H_B effects an 8% enhancement of the signal for H_A and a 1% enhancement of H_C. These results suggested that all three protons are cis related. The regiochemistry of the cycloadduct was assigned by considering the coupling pattern of the associated protons. In the ^{1}H NMR spectrum, H_A proton is a doublet whilst H_C proton appeared as an apparent triplet (coupling with CH_2 proton).

2. Experimental

2.1. General

Melting points were determined on a Reichert hot-stage apparatus and are uncorrected. Microanalysis was performed using a Carlo Erba MOD 1108 instrument. Mass spectrometric data were recorded on a V.G.-AutoSpec instrument operating at 70 eV in EI and used Cs ions for FAB spectra. Accurate molecular weights were recorded on a Micromass LCT KAIII electrospray (ES) machine. Infrared spectra were recorded on a Nicolet Magna FT-IR Spectrometer. Optical rotations were measured at ambient temperature using an AA1000 polarimeter. Nuclear magnetic resonance spectra were recorded at 250 MHz on a Bruker AC250 instrument or at 500 MHz on a Bruker DRX500 instrument. Chemical shifts (δ) are given in parts per million (ppm). Deuteriochloroform was used as the solvent unless otherwise stated. The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, dd=double doublet, dt=double triplet, ddd=double double doublet, m=multiplet, b=broad. Flash chromatography employed silica gel 60 (230–400 mesh). All solvents were purified according to standard procedures. The term ether refers to diethyl ether. Analytical grade anhydrous silver salts were used as purchased. In all reactions involving silver(I) salts the reaction flask was covered with aluminium foil.

2.2. General procedure for aldimines

A mixture of α-amino-γ-butyrolactone hydrobromide or α-amino-γ-butyrothiolactone hydrochloride (1.1 equiv), triethylamine (1.2 equiv) and anhydrous magnesium sulfate (5 g for each 1 g of hydrobromide salt) was stirred in dry dichloromethane for 1 h before the addition of the appropriate aldehyde (1 equiv). After stirring at room temperature for an appropriate time, the suspension was filtered and the filtrate washed with water (2×) to remove the triethylammonium bromide salt. The organic layer was separated, dried ($MgSO_4$), evaporated under reduced pressure and the residue triturated with ether to afford the solid imine. In the case of aliphatic aldimines the water wash was omitted and the residue triturated with ether to precipitate salts and then filtered. The filtrate was evaporated under reduced pressure to give the product as an oil. All the imines were used for the cycloaddition reactions without further purification due to their thermal and chromatographic instability.

2.2.1. (3-Pyridylmethylidene)-amino-dihydro-furan-2-one (7b). Compound **7b** was prepared from α-amino-γ-butyrolactone hydrobromide (2.00 g, 11.0 mmol), 3-pyridine

carboxaldehyde (1.03 mL, 11 mmol) and triethylamine (1.68 mL, 12.1 mmol) in DCM (35 mL) over 4 h. The crude imine (1.70 g, 81%) was a pale yellow viscous oil, which was used without further purification. δ (^{1}H, 250 MHz): 9.0 and 8.68 (2×m, 2×1H, pyridyl-H), 8.59 (s, 1H, CH═N) 8.12 and 7.36 (2×m, 2×1H, pyridyl-H), 4.68 and 4.48 (2×m, 2×1H, CH_2O), 4.35 (t, 1H, *J* 7.8 Hz, CHN) and 2.85–2.58 (m, 2H, CH_2CH_2O); *m/z* (%): 190 (M^+, 36), 145 (35), 144 (83), 131 (26), 118 (75), 107 (48), 105 (56), 92 (100), 86 (71) and 51 (55).

2.2.2. 3′-(*N*-Phenylsulfonyl-indolylmethylidene)-amino-dihydro-furan-2-one (7c). α-Amino-γ-butyrolactone (1.00 g, 5.49 mmol), *N*-sulfonyl-3-indolylcarboxaldehyde (1.56 g, 5.49 mmol) and triethylamine (0.8 mL, 6.0 mmol) in DCM (25 mL) were reacted over 4 h to afford the imine (1.50 g, 72.6%), which crystallised from ether as colourless needles, mp 130–132 °C. Found (HRMS, M^++H): 369.0910. $C_{19}H_{16}O_4N_2S$ requires: 369.0909; δ (^{1}H, 250 MHz): 8.56 (s, 1H, CH═N), 8.30 (m, 1H, indolyl-H), 7.98–7.89 (m, 4H, indolyl-H), 7.60–7.29 (m, 5H, phenyl-H), 4.63 (ddd, 1H, *J* 8.9, 7.6 and 5.2 Hz, CH_2O), 4.41 (m, 1H, CH_2O), 4.18 (t, 1H, *J* 7.7 Hz, CHN) and 2.69–2.59 (m, 2H, CH_2CH_2O); ν_{max} (film): 1773, 1638, 1447, 1369, 1269, 1219 and 1175 cm^{-1}; *m/z* (%): 368 (M^+, 29), 285 (64), 227 (8), 183 (38), 169 (17), 156 (34), 141 (53) and 77 (100).

2.2.3. (4-Biphenylmethylidene)-amino-dihydro-furan-2-one (7d). Compound **7d** was prepared from α-amino-γ-butyrolactone hydrobromide (1.00 g, 5.0 mmol), 4-biphenyl carboxaldehyde (0.91 g, 5.0 mmol) and triethylamine (0.85 mL, 6.04 mmol) in DCM (25 mL) over 6 h to afford the imine (0.74 g, 56%) as a colourless solid, mp 110–112 °C. Found (HRMS, M^++H): 266.1183. $C_{17}H_{15}O_2N$ requires: 266.1181; δ (^{1}H, 250 MHz): 8.46 (s, 1H, CH═N), 7.86–7.82 (m, 2H, phenyl-H), 7.67–7.61 (m, 4H, phenyl-H), 7.46–7.40 (m, 3H, phenyl-H), 4.62 (ddd, 1H, *J* 9.0, 7.4 and 5.2 Hz, CH_2O), 4.40 (m, 1H, CH_2O), 4.25 (dd, 1H, *J* 7.3 and 7.9 Hz, CHN) and 2.68–2.62 (m, 2H, CH_2CH_2O); ν_{max} (film): 1773, 1637, 1607, 1487, 1371, 1218, 1164, 1109 and 972 cm^{-1}; *m/z* (%): 265 (M^+, 9), 220 (25), 193 (36), 180 (39), 165 (44) and 86 (100).

2.2.4. 3-(Cyclohexylmethylidene)amino-dihydro-furan-2-one (7e). α-Amino-γ-butyrolactone hydrobromide (5.00 g, 27.5 mmol), triethylamine (4.2 mL, 30.2 mmol), cyclohexane carboxaldehyde (3.08 g, 27.5 mmol) and magnesium sulfate in DCM (100 mL) after 2 h gave the product (5.26 g, 98%) as a colourless oil, which was used without further purification for the subsequent cycloaddition reactions. Found (HRMS, M^++H): 196.1337. $C_{11}H_{17}O_2N$ requires: 196.1337; δ (^{1}H, 250 MHz): 7.69 (d, 1H, *J* 5.1 Hz, CH═N), 4.52 and 4.32 (2×m, 2×1H, CH_2O), 3.95 (t, 1H, *J* 8.1 Hz, CHN), 2.61–2.38 (m, 2H, CH_2CH_2O), 2.25 (m, 1H, cyclohexyl-H), and 1.93–1.65 and 1.38–1.16 (2×m, 2×5H, cyclohexyl-H); ν_{max} (film): 2926, 2852, 1776, 1695, 1662, 1449, 1371, 1218 and 1165 cm^{-1}; *m/z* (%): 195 (M^+, 3), 180 (1), 166 (5), 153 (5), 140 (71), 127 (100) and 86 (66).

2.2.5. 3-(3′-Cyclohexenylmethylidene)amino-dihydro furan-2-one (7f). Compound **7f** was prepared from α-amino-γ-butyrolactone (2.00 g, 11 mmol), racemic 1,2,3,6-tetrahydrobenzaldehyde (1.29 mL, 11.0 mmol) and triethylamine (1.7 mL, 12.0 mmol) in DCM (40 mL) stirring for 8 h. The crude imine (2.11 g, 99%) was obtained as a pale yellow oil, which was used without further purification. Found (HRMS, M^++H): 194.1184. $C_{11}H_{15}O_2N$ requires: 194.1181; δ (^{1}H, 250 MHz): 7.79 (d, 1H, *J* 4.9 Hz, CH═N), 5.71 (br s, 2H, olefinic-H), 4.52 and 4.34 (2×m, 2×1H, CH_2O), 3.99 (t, 1H, *J* 8.1 Hz, CHN), 2.63–2.39 (m, 3H, CH_2CH_2O and cyclohexenyl-H), 2.26–1.87 (m, 5H, cyclohexenyl-H) and 1.58 (m, 1H, cyclohexenyl-H); ν_{max} (film): 2917, 2839, 1775, 1696, 1663, 1437, 1371, 1276 and 1163 cm^{-1}; *m/z* (%): 193 (M^+, 11), 164 (8), 148 (5), 134 (14), 127 (23), 120 (20), 108 (100), 102 (13), 91 (46) and 77 (26).

2.2.6. 3-(*N*-Citronellylidene)amino-dihydro-furan-2-one (7g). α-Amino-γ-butyrolactone hydrobromide (3.00 g, 16.5 mmol), triethylamine (2.5 mL, 18.1 mmol) and (*R*)-(+)-citronellal (3.0 mL, 16.5 mmol) were reacted for 4 h. Work-up gave the product (3.10 g, 80%) as a pale yellow oil, which was used without further purification for the subsequent cycloaddition reactions. Found (HRMS, M^++H): 238.1808. $C_{14}H_{23}O_2N$ requires: 238.1807; δ (^{1}H, 250 MHz): 7.83 (d, 1H, *J* 4.9 Hz, CH═N), 5.08 (m, 1H, olefinic-H), 4.52 and 4.32 (2×m, 2×1H, CH_2O), 4.0 (t, 1H, *J* 8.0 Hz, CHN), 2.58–2.49 (m, 2H, CH_2CH_2O), 2.04–1.70 (m, 4H, aliphatic-H), 1.68 and 1.60 (2×s, 2×3H, Me_2C═C), 1.55–1.16 (m, 3H, aliphatic-H) and 0.97 and 0.95 (d, 3H, *J* 4.0 Hz, CH_3CH); ν_{max} (film): 2960, 2917, 1778, 1696, 1448, 1376, 1217, 1167 and 1055 cm^{-1}; *m/z* (%): 237 (M^+, 2), 222 (4), 194 (6), 154 (100), 121 (47) and 69 (33).

2.2.7. 3-(8,8-Dimethyl-1,2,3,4,5,6,7,8-octahydronaphthalen-2-yl)methylidene amino-dihydrofuran-2-one (7h). α-Amino-γ-butyrolactone hydrobromide (2.00 g, 11.0 mmol), cyclemone (2.13 g, 11.0 mmol), triethylamine (1.7 mL, 12.1 mmol) and magnesium sulfate in DCM (50 mL) after 7 h gave the product (2.9 g, 95%) as a colourless oil, which was used without further purification for the subsequent cycloaddition reactions. Found (HRMS, M^++H): 276.1965. $C_{17}H_{25}O_2N$ requires: 276.1963; δ (^{1}H, 250 MHz): 7.76 (m, 1H, CH═N), 4.52 and 4.34 (2×m, 2×1H, CH_2O), 3.98 (t, 1H, *J* 7.9 Hz, CHN), 2.57–2.39 (m, 2H, CH_2CH_2O), 2.13–1.37 (m, 10H, aliphatic-H) and 1.18–0.82 (m, 8H, aliphatic-H and 2×CH_3); ν_{max} (film): 2925, 2866, 1777, 1695, 1663, 1456, 1360, 1217 and 1165 cm^{-1}; *m/z* (%): 275 (M^+, 36), 260 (37), 206 (11), 190 (100), 174 (44) 159 (65) and 104 (86).

2.2.8. 3-[4-(4-Methylpent-3-enyl)-cyclohex-3-en-1-yl]-methylidene-amino-dihydrofuran-2-one (7i). Compound **7i** was prepared from α-amino-γ-butyrolactone (3.00 g, 16.5 mmol), racemic emfetal (3.20 g, 16.5 mmol), triethylamine (2.5 mL, 18.1 mmol) and magnesium sulfate in DCM (70 mL) over 8 h. The crude imine (4.25 g, 93%) was obtained as a pale yellow oil, which was used without further purification. Found (HRMS, M^++H): 276.1960. $C_{17}H_{25}O_2N$ requires: 276.1963; δ (^{1}H, 250 MHz): 7.77 (d, 1H, *J* 4.9 Hz, CH═N), 5.41 (br, 1H, olefinic-H), 5.08 (m, 1H, olefinic-H), 4.52 and 4.34 (2×m, 2×1H, CH_2O), 3.98 (t, 1H, *J* 8.0 Hz, CHN), 2.56–2.40 (m, 2H, CH_2CH_2O), 2.20–1.94 (m, 10H, aliphatic-H), 1.65 and 1.50 (2×s, 2×3H, 2×CH_3) and 1.45 (m, 1H, aliphatic-H); ν_{max} (film): 2916, 1778, 1662, 1438, 1373, 1217, 1164 and 1104 cm^{-1}; *m/z* (%): 275 (M^+, 15), 206 (40), 190 (31), 121 (29), 105 (100) and 69 (61).

2.2.9. 3-[3-(4-Isopropylphenyl)-2-methylpropylidene]-amino-dihydrofuran-2-one (7j). α-Amino-γ-butyrolactone hydrobromide (3.00 g, 16.5 mmol), cyclamen aldehyde (3.13 g, 16.5 mmol), triethylamine (2.5 mL, 18.1 mmol) and magnesium sulfate in DCM (50 mL) after 8 h gave the product (4.4 g, 95%) as a colourless oil, which was used without further purification for the subsequent cycloaddition reactions. Found (HRMS, M^++H): 274.1806. $C_{17}H_{23}O_2N$ requires: 274.1807; δ (^{1}H, 250 MHz): 7.79 and 7.73 (d, 1H, *J* 4.9 Hz, CH═N), 7.16–7.07 (m, 4H, phenyl-H), 4.48 and 4.30 (2×m, 2×1H, CH_2O), 3.94 (t, 1H, *J* 8.2 Hz, CHN), 2.94–2.84 (m, 2H, C*H*$_2$CH$_2$O), 2.69–2.35 (m, 4H, aliphatic-H), 1.23 (d, 2×3H, *J* 7.0 Hz, 2×CH_3), and 1.10 and 1.17 (d, 3H, *J* 6.0 Hz, CH_3); ν_{max} (film): 2960, 2928, 2871, 1778, 1695, 1663, 1513, 1457 and 1366 cm^{-1}; *m*/*z* (%): 273 (M^+, 51), 258 (61), 214 (7), 200 (21), 188 (100), 172 (24), 157 (34) and 133 (78).

2.2.10. 3-(3-Methyl-5-phenylpentylidene)amino-dihydrofuran-2-one (7k). Compound **7k** was prepared from α-amino-γ-butyrolactone (3.00 g, 16.5 mmol), racemic mefanal (2.90 g, 16.5 mmol), triethylamine (2.5 mL, 18.1 mmol) and magnesium sulfate in DCM (70 mL) over 8 h. The crude imine (3.95 g, 92%) was obtained as a pale yellow oil, which was used without further purification. δ (^{1}H, 250 MHz): 7.82 (t, 1H, *J* 5.2 Hz, CH═N), 7.31–7.16 (m, 5H, phenyl-H), 4.51 and 4.30 (2×m, 2×1H, CH_2O), 3.99 (t, 1H, *J* 8.1 Hz, CHN), 2.89–2.15 (m, 6H, C*H*$_2$CH$_2$O and aliphatic-H), 1.94–1.43 (m, 3H, aliphatic-H), and 1.04 and 1.01 (d, 3H, *J* 4.5 Hz, CH_3); *m*/*z* (%): 259 (M^+, 1.5), 244 (4), 216 (3), 174 (20), 154 (91), 143 (12), 127 (63) and 91 (100).

2.2.11. 3-(3-Phenylbutylidene)amino-dihydrofuran-2-one (7l). α-Amino-γ-butyrolactone hydrobromide (2.00 g, 11.0 mmol), 3-phenylbutyraldehyde (1.5 mL, 10.0 mmol), triethylamine (1.7 mL, 12.1 mmol) and magnesium sulfate in DCM (50 mL) after 2 h gave the product (2.20 g, 95%) as a colourless oil, which was used without further purification for the subsequent cycloaddition reactions. Found (HRMS, M^++H): 232.1333. $C_{14}H_{17}O_2N$ requires: 232.1337; δ (^{1}H, 250 MHz): 7.75–7.69 (m, 1H, CH═N), 7.36–7.16 (m, 5H, phenyl-H), 4.47 and 4.26 (2×m, 2×1H, CH_2O), 3.97 (m, 1H, CHN), 3.12 (m, 1H, aliphatic-H), 2.72–2.28 (m, 4H, C*H*$_2$CH$_2$O and olefinic-H), 1.34 and 1.32 (d, 3H, *J* 2.8 Hz, CH_3) and 1.21 (m, 1H, aliphatic-H); ν_{max} (film): 2961, 1774, 1696, 1663, 1602, 1494, 1452, 1372 and 1277 cm^{-1}; *m*/*z* (%): 231 (M^+, 4.5), 216 (44), 172 (6), 146 (36) 130 (51), 105 (100), 86 (25) and 41 (29).

2.2.12. 3-(3-Phenylpropylidene)amino-dihydrofuran-2-one (7m). Compound **7m** was prepared from α-amino-γ-butyrolactone (1.00 g, 5.5 mmol), 3-phenyl propionaldehyde (0.66 mL, 5.0 mmol), triethylamine (0.85 mL, 6.0 mmol) and magnesium sulfate in DCM (25 mL) over 2 h. The crude imine (1.00 g, 92%) was a pale yellow oil, which was used without further purification. Found (HRMS, M^++H): 218.1180. $C_{13}H_{15}O_2N$ requires: 218.1181; δ (^{1}H, 250 MHz): 7.88 (m, 1H, CH═N), 7.30–7.19 (m, 5H, phenyl-H), 4.51 and 4.30 (2×m, 2×1H, CH_2O), 3.99 (t, 1H, *J* 8.2 Hz, CHN) and 2.91–2.36 (m, 6H, C*H*$_2$CH$_2$O and aliphatic-H); ν_{max} (film): 2918, 1774, 1696, 1663, 1602, 1496, 1453, 1371 and 1276 cm^{-1}; *m*/*z* (%): 217 (M^+, 9), 158 (10), 132 (77), 117 (57) and 91 (100).

2.2.13. *tert*-Butyl (1*S*)-1-benzyl-2-(2-oxotetrahydrofuran-3-yl)imino-ethylcarbamate (7n). α-Amino-γ-butyrolactone hydrobromide (0.80 g, 4.4 mmol), (*S*)-Boc-L-phenylalaninal (1.00 g, 4.0 mmol), triethylamine (0.67 mL, 4.8 mmol) and magnesium sulfate in DCM (20 mL) after 2 h gave the product (1.31 g, 98%) as a colourless oil, which was used without further purification for the subsequent cycloaddition reactions. δ (^{1}H, 250 MHz): 7.80 (m, 1H, CH═N), 7.31–7.18 (m, 5H, phenyl-H), 5.25 (b, 1H, NH), 4.63–4.19 (m, 3H, NHC*H* and CH_2O), 4.04 (m, 1H, CHN), 3.10–2.95 (m, 2H, aliphatic-H), 2.58–2.41 (m, 2H, C*H*$_2$CH$_2$O) and 1.45 (s, 3×3H, 3×CH_3); *m*/*z* (%): 332 (M^+, <1), 276 (11), 258 (9), 141 (47), 120 (47), 91 (58) and 57 (100).

2.2.14. 3-[3-(1,3-Benzodioxol-5-yl)-2-methylpropylidine]-amino-dihydrofuran-2-one (7o). α-Amino-γ-butyrolactone (1.00 g, 5.49 mmol), racemic 2-methyl-3-(3,4-methylenedioxy phenyl)propanal (0.91 mL, 5.5 mmol), triethylamine (0.85 mL, 6.0 mmol) and magnesium sulfate in DCM (30 mL) after 4 h gave the product (1.41 g, 94%) as a colourless oil, which was used without further purification for the subsequent cycloaddition reactions. Found (HRMS, M^++H): 276.1238. $C_{15}H_{17}O_4N$ requires: 276.1236; δ (^{1}H, 250 MHz): 7.77 and 7.73 (d, 1H, *J* 4.8 Hz, CH═N), 6.74–6.59 (m, 4H, phenyl-H), 5.92 (s, 2H, OCH_2O), 4.50 and 4.30 (2×m, 2×1H, CH_2O), 3.98 (m, 1H, CHN), 2.98–2.35 (m, 5H, C*H*$_2$CH$_2$O and aliphatic-H), and 1.09 and 1.06 (d, 3H, *J* 5.0 Hz, CH_3); ν_{max} (film): 2915, 1774, 1695, 1662, 1502, 1489, 1441, 1369 and 1246 cm^{-1}; *m*/*z* (%): 275 (M^+, 14), 260 (13), 202 (9), 190 (51), 135 (100), 105 (13) and 77 (35).

2.2.15. 3-(2-Naphthylidine)-amino-dihydrofuran-2-one (7p). α-Amino-γ-butyrolactone (3.00 g, 16.4 mmol), naphthalene-2-carboxaldehyde (1.70 mL, 11.0 mmol), triethylamine (2.50 mL, 18.1 mmol) and magnesium sulfate in DCM (50 mL) after 4 h gave the product (1.95 g, 74%) as colourless plates, mp 135–137 °C. Found: C, 75.00; H, 5.25; N, 5.65. $C_{15}H_{13}O_2N$ requires: C, 75.30; H, 5.50; N, 5.85%; δ (^{1}H, 250 MHz): 8.58 (s, 1H, CH═N), 8.09 (s, 1H, ArH), 8.01–7.84 (m, 4H, ArH), 7.56–7.51 (m, 2H, ArH), 4.64 (ddd, 1H, *J* 5.3 and 9.0 Hz, OCH_2), 4.44 (m, 1H, OCH_2), 4.28 (dd, 1H, *J* 0.5 and 7.8 Hz, CHN) and 2.71–2.60 (m, 5H, C*H*$_2$CH$_2$O); ν_{max} (film): 2876, 1770, 1636, 1370, 1218, 1168 and 1020 cm^{-1}; *m*/*z* (ES$^+$, %): 240 (M^++H, 100), 212 (32).

2.2.16. 3-(8,8-Dimethyl-1,2,3,4,5,6,7,8-octahydronaphthalen-2-yl)methylidene amino-dihydrothiophen-2-one (8a). α-Amino-γ-butyrothiolactone hydrochloride (2.00 g, 13.0 mmol), cyclemone aldehyde (2.50 g, 13.0 mmol), triethylamine (2 mL, 14.3 mmol) and magnesium sulfate in DCM (60 mL) after 4 h gave the product (3.60 g, 95%) as a pale yellow gum, which was used without further purification for the subsequent cycloaddition reactions. δ (^{1}H, 250 MHz): 7.66 (d, 1H, *J* 5.4 Hz, CH═N), 3.84 (m, 1H, CHN), 3.48 and 3.34 (2×m, 2×1H, CH_2S), 2.60–2.44 (m, 2H, C*H*$_2$CH$_2$S), 2.17–1.21 (m, 13H, aliphatic-H) and 0.96 (s, 2×3H, 2×CH_3); *m*/*z* (%): 291 (M^+, 7), 263 (23), 248 (21), 190 (49), 175 (73), 91 (85) and 41 (100).

2.2.17. 3-[4-(4-Methylpent-3-enyl)-cyclohex-3-en-1-yl]-methylidene-amino-dihydrothiophen-2-one (8b). α-Amino-γ-butyrothiolactone hydrochloride (1.00 g, 6.51 mmol),

emfetal (1.25 g, 6.5 mmol), triethylamine (1.0 mL, 7.2 mmol) and magnesium sulfate in DCM (25 mL) after 4 h gave the product (1.71 g, 90%) as a pale yellow oil, which was used without further purification for the subsequent cycloaddition reactions. δ (^{1}H, 250 MHz): 7.67 (d, 1H, *J* 5.1 Hz, CH=N), 5.40 and 5.11 (2×m, 2×1H, olefinic-H), 3.84 (dd, 1H, *J* 8.6 and 6.8 Hz, CHN), 3.50 and 3.35 (2×m, 2×1H, CH_2S), 2.55–2.39 (m, 2H, CH_2CH_2S), 2.08–1.87 (m, 11H, aliphatic-H) and 1.68 and 1.60 (2×s, 2×3H, 2×CH_3); *m/z* (%): 291 (M^+, 4), 263 (11), 222 (39), 194 (36), 105 (66), 69 (91) and 41 (100).

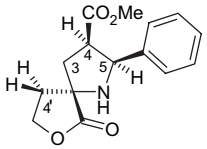
2.2.18. 3-[3-(4-Isopropylphenyl)-2-methylpropylidene]-amino-dihydrothiophen-2-one (8c). α-Amino-γ-butyrothiolactone hydrochloride (1.00 g, 6.5 mmol), cyclamen aldehyde (1.24 g, 6.5 mmol), triethylamine (1.0 mL, 7.2 mmol) and magnesium sulfate in DCM (25 mL) after 4 h gave the product (1.63 g, 86%) as a colourless oil, which was used without further purification for the subsequent cycloaddition reactions. δ (^{1}H, 250 MHz): 7.70 and 7.67 (d, 1H, *J* 5.1 Hz, CH=N), 7.16–7.06 (m, 4H, phenyl-H), 3.81 (m, 1H, CHN), 3.52–3.24 (m, 2H, CH_2S), 2.95–2.83 (m, 2H, CH_2CH_2S), 2.71–2.27 (m, 4H, aliphatic-H), 1.24 and 1.21 (2×d, 2×3H, *J* 6.9 Hz, 2×CH_3) and 1.08 and 1.05 (d, 3H, *J* 6.6 Hz, CH_3); *m/z* (%): 289 (M^+, 8), 274 (13), 261 (11), 200 (31), 133 (100), 117 (77), 91 (80) and 41 (68).

2.2.19. *N*-3-[Chloro-5-(trifluoromethyl)pyridin-2-yl]-methyl-*N*-phenylmethylidene amine (15). 2-Aminomethyl-3-chloro-5-(trifluoromethyl)pyridine hydrochloride (0.50 g, 2.0 mmol), benzaldehyde (0.20 mL, 2.0 mmol), triethylamine (0.31 mL, 2.2 mmol) and magnesium sulfate in DCM (25 mL) after 1 h gave the product (0.55 g, 91%) as a colourless oil, which was used without further purification for the subsequent cycloaddition reactions. δ (^{1}H, 250 MHz): 8.77 (d, 1H, *J* 1.0 Hz, pyridyl-H), 8.51 (s, 1H, CH=N), 7.95 (d, 1H, 1.8 Hz, pyridyl-H), 7.91–7.26 (m, 5H, phenyl-H) and 5.12 (s, 2H, NCH_2); *m/z* (%, FAB): 301 (M^++1, 31), 299 (M^++1, 100), 284 (8), 282 (20), 196 (6), 194 (22) and 91 (7).

2.3. General procedure for silver(I) catalysed cycloaddition reactions

Aldimine (1.0 equiv), triethylamine (1.1 equiv), dipolarophile (1.1 equiv) and silver acetate (1.5 equiv) were mixed in anhydrous acetonitrile. Silver oxide (10 mol %) and toluene (dried over sodium wire) were used in the case of aliphatic aldimines. The resulting suspension was stirred for an appropriate period (see below) at room temperature (monitored by TLC and ^{1}H NMR). After completion of the reaction the mixture was quenched with saturated aqueous ammonium chloride and extracted with ether or dichloromethane (2×). The dried (magnesium sulfate) organic layer was evaporated under reduced pressure. The ratio of any isomers present in the residue was calculated from the integrals of appropriate peaks in the ^{1}H NMR spectra. Flash chromatography of the residue afforded the product.

2.3.1. Methyl 6-oxo-2-phenyl-7-oxa-1-azaspiro[4.4]-nonane-3-carboxylate (9a). A mixture of imine **7a** (2.00 g, 10.6 mmol), triethylamine (1.60 mL, 11.6 mmol), methyl acrylate (1.14 mL, 12.7 mmol) and silver acetate (2.64 g, 15.8 mmol) were stirred in acetonitrile (70 mL) over 4 h. Flash chromatography eluting with ether afforded the product (2.50 g, 86%) as a colourless solid, which crystallised from dichloromethane/hexane as colourless plates, mp 103–105 °C. Found: C, 65.45; H, 6.15; N, 5.00. $C_{15}H_{17}O_4N$ requires: C, 65.45; H, 6.20; N, 5.10%; δ (^{1}H, 250 MHz): 7.43–7.23 (m, 5H, ArH), 4.64 (t, 1H, *J* 7.1 Hz, NHC*H*), 4.46 (ddd, 1H, *J* 3.8, 7.6 and 9.2 Hz, CH_2O), 4.25 (dt, 1H, *J* 6.8 and 9.0 Hz, CH_2O), 3.52 (dt, 1H, *J* 7.4 and 9.2 Hz, C*H*CO_2Me), 3.25 (s, 3H, OMe), 2.76 (d, 1H, *J* 5.0 Hz, NH), 2.55 (dd, 1H, *J* 9.7 and 12.8 Hz, CH_2CHCO_2Me), 2.43–2.26 (m, 2H, CH_2CH_2O) and 2.14 (dd, 1H, *J* 7.4 and 12.8 Hz, CH_2CHCO_2Me); ν_{max} (film): 2949, 1770, 1733, 1495, 1455, 1436, 1373, 1281 and 1180 cm^{-1}; *m/z* (%): 275 (M^+, 0.6), 244 (18), 231 (100), 217 (40), 177 (42), 172 (76), 158 (79), 143 (25) and 91 (31).



NOE data for **9a**:

Signal irradiated	Enhancement (%)					
	5-H	4-H	NH	3-H	Ar-H	3′-H
5-H		9.5	2.0	2.9	10.0	2.9
4-H	10.0		—	3.9	—	2.3

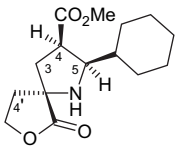
2.3.2. Methyl 6-oxo-2-phenyl-7-oxa-1-azaspiro[4.4]-nonane-3-carboxylate (9b). Methyl acrylate (114 μl, 1.26 mmol) was added to a mixture of imine **7b** (200 mg, 1.05 mmol), triethylamine (0.16 mL, 1.15 mmol) and silver acetate (0.26 g, 1.57 mmol) in acetonitrile (10 mL) and the resulting mixture was stirred at room temperature for 4 h. After work-up, the residue was subjected to flash chromatography eluting with ether to afford the product (0.14 g, 48%) as pale yellow plates, mp 147–149 °C. Found: C, 60.70; H, 6.00; N, 10.10. $C_{14}H_{16}O_4N_2$ requires: C, 60.85; H, 5.85; N, 10.15%; δ (^{1}H, 250 MHz): 8.53–8.50 (m, 2H, pyridyl-H), 7.99 and 7.31 (2×m, 2×1H, pyridyl-H), 4.72 (d, 1H, *J* 8.6 Hz, NHC*H*), 4.46 (m, 1H, CH_2O), 4.27 (dt, 1H, *J* 7.9 and 9.0 Hz, CH_2O), 3.58 (ddd, 1H, *J* 7.4, 8.6 and 10.1 Hz, C*H*CO_2Me), 3.32 (s, 3H, OMe), 2.58 (dd, 1H, *J* 10.3 and 12.9 Hz, CH_2CHCO_2Me), 2.37–2.31 (m, 2H, CH_2CH_2O), 2.17 (dd, 1H, *J* 7.2 and 12.9 Hz, CH_2CHCO_2Me) and 2.05 (b, 1H, NH); ν_{max} (film): 2950, 1769, 1733, 1684, 1652, 1576, 1558, 1480, 1456, 1373, 1289 and 1153 cm^{-1}; *m/z* (%): 276 (M^+, 1.8), 245 (18), 232 (100), 218 (38), 173 (59), 159 (66), 145 (16), 118 (26) and 91 (18).

2.3.3. Methyl 6-oxo-2-(3-*N*-sulfonyl-indolyl)-7-oxa-1-azaspiro[4.4]nonane-3-carboxylate (9c). A mixture of imine **7c** (200 mg, 0.54 mmol), triethylamine (0.08 mL, 0.6 mmol), methyl acrylate (0.06 mL, 0.65 mmol) and silver acetate (0.13 g, 0.8 mmol) in acetonitrile (15 mL) was stirred over 24 h. Work-up followed by flash chromatography eluting with ether afforded the product (132 mg, 54%) as a colourless solid, which crystallised from dichloromethane/hexane as colourless plates, mp 75–77 °C. Found: C, 60.80; H, 4.85; N, 6.00; S, 7.15. $C_{23}H_{22}O_6N_2S$ requires: C, 60.75; H, 4.90; N, 6.20; S, 7.05%; δ (^{1}H, 250 MHz): 8.00–7.19 (m, 10H, ArH and indolyl-H), 4.87 (d, 1H,

J 7.8 Hz, NHC*H*), 4.47 (ddd, 1H, *J* 4.0, 7.2 and 9.3 Hz, CH_2O), 4.28 (dt, 1H, *J* 6.9 and 8.9 Hz, CH_2O), 3.56 (dt, 1H, *J* 7.4 and 9.3 Hz, C*H*CO_2Me), 2.90 (s, 3H, OMe), 2.70 (b, 1H, NH), 2.62 (dd, 1H, *J* 9.4 and 13.0 Hz, CH_2CHCO_2Me), 2.38–2.31 (m, 2H, CH_2CH_2O) and 2.20 (dd, 1H, *J* 7.2 and 13.0 Hz, CH_2CHCO_2Me); ν_{max} (film): 1771, 1733, 1653, 1559, 1447, 1437, 1367, 1214 and 1123 cm^{-1}; *m*/*z* (%): 454 (M^+, 11), 410 (11), 368 (80), 356 (35), 313 (13), 269 (35), 255 (21), 227 (100) and 183 (34).

2.3.4. Methyl 2-(1.1′-biphenyl-4-yl)-6-oxo-7-oxa-1-azaspiro[4.4]nonane-3-carboxylate (9d). A mixture of imine **7d** (0.25 g, 0.94 mmol), triethylamine (0.15 mL, 1.03 mmol), methyl acrylate (0.10 mL, 1.13 mmol) and silver acetate (0.23 g, 1.41 mmol) in acetonitrile (15 mL) was stirred for 18 h. Work-up followed by flash chromatography eluting with ether afforded the product (0.19 g, 57%) as a colourless solid, which crystallised from dichloromethane/hexane as colourless plates, mp 125–127 °C. Found: C, 72.00; H, 6.15; N, 3.85. $C_{21}H_{21}O_4N$ requires: C, 71.80; H, 6.00; N, 4.00%; δ (^{1}H, 250 MHz): 7.60–7.26 (m, 9H, phenyl-H), 4.68 (d, 1H, *J* 8.3 Hz, NHC*H*), 4.45 and 4.28 (2×m, 2×1H, CH_2O), 3.56 (m, 1H, CHCO_2Me), 3.28 (s, 3H, OMe), 2.77 (b, 1H, NH), 2.63 (dd, 1H, *J* 9.8 and 12.8 Hz, CH_2CHCO_2Me), 2.38–2.30 (m, 2H, CH_2CH_2O) and 2.16 (dd, 1H, *J* 7.3 and 12.8 Hz, CH_2CHCO_2Me); ν_{max} (film): 1771, 1734, 1487, 1436, 1373, 1216, 1194 and 1086 cm^{-1}; *m*/*z* (%): 351 (M^+, 1.5), 320 (17), 307 (100), 293 (39), 248 (89), 219 (43) and 165 (66).

2.3.5. Methyl 2-cyclohexyl-6-oxo-7-oxa-1-azaspiro[4.4]-nonane-3-carboxylate (9e). A mixture of imine **7e** (1.00 g, 5.11 mmol), triethylamine (0.78 mL, 5.62 mmol), silver oxide (118 mg, 0.51 mmol) and methyl acrylate (0.55 mL, 6.13 mmol) in toluene (50 mL) was stirred at room temperature for 4 h. Work-up without the need for chromatography gave the product (1.28 g, 89%), which crystallised from dichloromethane/hexane as colourless plates, mp 88–90 °C. Found: C, 64.30; H, 8.15; N, 4.75. $C_{15}H_{23}O_4N$ requires: C, 64.05; H, 8.25; N, 5.00%; δ (^{1}H, 250 MHz): 4.40 (dt, 1H, *J* 4.2 and 8.4 Hz, CH_2O), 4.23 (dt, 1H, *J* 6.7 and 8.6 Hz, CH_2O), 3.71 (s, 3H, OMe), 3.14 (ddd, 1H, *J* 4.0, 6.5 and 8.4 Hz, CHCO_2Me), 2.86 (dd, 1H, *J* 6.7 and 9.5 Hz, NHC*H*), 2.40–2.07 (m, 4H, CH_2CHCO_2Me and CH_2CH_2O) and 1.73–1.15 (m, 12H, NH and cyclohexyl-H); ν_{max} (film): 2923, 2851, 1773, 1728, 1436, 1370, 1211, 1170 and 1126 cm^{-1}; *m*/*z* (%): 282 (M^++1, 8), 250 (5), 237 (34), 223 (13), 198 (86), 154 (100), 140 (52) and 94 (29). In NOE 4′-H proton was overlapped with cyclohexyl protons.



NOE data for **9e**:

Signal irradiated	Enhancement (%)			
	5-H	4-H	3-H	Aliphatic-H
5-H		6.8	2.9	13.0
4-H	4.1		5.9	2.3

2.3.6. Methyl 2-(3-cyclohexen-1-yl)-6-oxo-7-oxa-1-azaspiro[4.4]nonane-3-carboxylate (9f). A mixture of imine **7f** (1.00 g, 5.17 mmol), triethylamine (0.80 mL, 5.68 mmol), silver oxide (0.12 g, 0.517 mmol) and methyl acrylate (0.56 mL, 6.2 mmol) in toluene (50 mL) was stirred for 2 h. Work-up followed by flash chromatography eluting with ether afforded the product (0.83 g, 57%) as a 1:1 mixture of diastereomers, which crystallised from dichloromethane/hexane as colourless plates, mp 84–90 °C. Found: C, 64.50; H, 7.55; N, 4.85. $C_{15}H_{21}O_4N$ requires: C, 64.50; H, 7.60; N, 5.00%; δ (^{1}H, 250 MHz): 5.70–5.57 (m, 2H, olefinic-H), 4.42 (dt, 1H, *J* 4.0 and 8.3 Hz, CH_2O), 4.23 (ddd, 1H, *J* 1.2, 7.3 and 9.0 Hz, CH_2O), 3.71 (s, 3H, OMe), 3.25–3.09 (m, 1H, CHCO_2Me), 2.97 (b, 1H, NHC*H*) and 2.43–1.22 (m, 12H, NH, CH_2CH_2O, CH_2CHCO_2Me and cyclohexenyl-H); ν_{max} (film): 2912, 1773, 1727, 1652, 1456, 1436, 1290, 1103 and 1079 cm^{-1}; *m*/*z* (%): 279 (M^+, 7), 235 (23), 221 (10), 198 (100), 176 (32), 166 (45), 154 (97), 140 (60), 94 (50), 80 (41), 67 (27) and 53 (19).

2.3.7. Methyl 2-(2,6-dimethyl-5-heptenyl)-6-oxo-7-oxa-1-azaspiro[4.4]nonane-3-carboxylate (9g). A mixture of imine **7g** (700 mg, 2.95 mmol), triethylamine (0.45 mL, 3.24 mmol), silver oxide (0.068 g, 0.29 mmol) and methyl acrylate (0.30 mL, 3.54 mmol) in toluene (30 mL) was stirred for 4 h. Work-up followed by flash chromatography eluting with ether afforded the product (0.25 g, 26%) as a colourless oil, which comprised a 1:1 mixture of diastereomers. Found: C, 67.00; H, 8.85; N, 4.60. $C_{15}H_{21}O_4N$ requires: C, 66.85; H, 9.05; N, 4.60%; δ (^{1}H, 250 MHz): 5.08 (m, 1H, olefinic-H), 4.40 (ddd, 1H, *J* 4.0, 8.1 and 8.9 Hz, CH_2O), 4.22 (dt, 1H, *J* 6.9 and 8.7 Hz, CH_2O), 3.70 (s, 3H, OMe), 3.42 (m, 1H, CHCO_2Me), 3.12 (m, 1H, NHC*H*), 2.45–1.86 (m, 7H, NH, CH_2CH_2O, CH_2CHCO_2Me and citronellyl-H), 1.68 and 1.60 (2×s, 2×3H, Me_2C=C), 1.55–1.13 (m, 3H, citronellyl-H) and 0.95 and 0.90 (d, 3H, *J* 6.5 Hz, citronellyl-CH_3); ν_{max} (film): 2954, 2916, 1773, 1733, 1436, 1375, 1213, 1171, 1117, 1069 and 1019 cm^{-1}; *m*/*z* (%): 323 (H^+, 9), 279 (12), 264 (13), 238 (54), 220 (69), 206 (21), 194 (55), 180 (31), 168 (76), 154 (100), 140 (39) and 94 (60).

2.3.8. Methyl 2-(8,8-dimethyl-1,2,3,4,5,6,7,8-octahydro-2-naphthalenyl)-6-oxo-7-oxa-1-azaspiro[4.4]nonane-3-carboxylate (9h). A mixture of imine **7h** (1.00 g, 3.6 mmol), triethylamine (0.55 mL, 3.9 mmol), silver oxide (0.08 g, 0.36 mmol) and methyl acrylate (0.40 mL, 4.3 mmol) in toluene (40 mL) was stirred for 3 h. Work-up followed by flash chromatography eluting with 2:1 v/v ether/hexane afforded the product (0.68 g, 52%) as colourless gum, which comprised a 1:1 mixture of diastereomers. Found: C, 70.05; H, 8.90; N, 3.70. $C_{21}H_{31}O_4N$ requires: C, 69.80; H, 8.65; N, 3.90%; δ (^{1}H, 250 MHz): 4.41 and 4.22 (2×m, 2×1H, CH_2O), 3.70 and 3.69 (s, 3H, OMe), 3.18 (m, 1H, CHCO_2Me), 2.94 (m, 1H, NHC*H*), 2.44–2.08 (m, 5H, NH, CH_2CH_2O and CH_2CHCO_2Me), 2.0–1.25 (m, 13H, aliphatic-H) and 0.95 (s, 2×3H, 2×CH_3); ν_{max} (film): 2924, 1774, 1728, 1436, 1371, 1211 and 1169 cm^{-1}; *m*/*z* (%): 361 (M^+, 14), 317 (6), 258 (5), 224 (12), 198 (100) and 154 (36).

2.3.9. Methyl 2-[4-(4-methyl-3-pentenyl)-3-cyclohexen-1-yl]-6-oxo-7-oxa-1-azaspiro[4.4]nonane-3-carboxylate (9i). A mixture of imine **7i** (1.50 g, 5.4 mmol), triethylamine

(0.83 mL, 5.9 mmol), silver oxide (0.12 g, 0.54 mmol) and methyl acrylate (0.60 mL, 6.5 mmol) in toluene (50 mL) was stirred for 4 h. Work-up followed by flash chromatography eluting with 4:1 v/v ether/hexane afforded the product (1.58 g, 81%) as a colourless oil, which comprised a 1:1 mixture of diastereomers. Found: C, 69.90; H, 8.90; N, 3.60. $C_{21}H_{31}O_4N$ requires: C, 69.80; H, 8.65; N, 3.90%; δ (^{1}H, 250 MHz): 5.38 and 5.36 (m, 1H, cyclohexenyl olefinic-H), 5.08 (m, 1H, olefinic-H), 4.42 and 4.22 (2×m, 2×1H, CH_2O), 3.71 and 3.70 (s, 3H, OMe), 3.16 (m, 1H, $CHCO_2Me$), 2.96 (m, 1H, NHC*H*), 2.46–1.90 (m, 15H, NH, C*H*$_2$CH$_2$O, C*H*$_2$CHCO$_2$Me and aliphatic-H), 1.68 and 1.59 (2×s, 2×3H, 2×CH_3) and 1.36 (m, 1H, aliphatic-H); ν_{max} (film): 2914, 1774, 1729, 1436, 1373, 1290, 1211, 1169 and 1110 cm^{-1}; *m*/*z* (%): 361 (M$^+$, 19), 292 (37), 258 (7), 248 (18), 198 (100), 166 (34) and 140 (24).

2.3.10. Methyl 2-[2-(4-isopropylphenyl)-1-methylethyl]-6-oxo-2-phenyl-7-oxa-1-azaspiro[4.4]nonane-3-carboxylate (9j). A mixture of imine **7j** (1.00 g, 3.6 mmol), triethylamine (0.56 mL, 4.0 mmol), silver oxide (0.08 g, 0.36 mmol) and methyl acrylate (0.40 mL, 4.4 mmol) in toluene (40 mL) was stirred for 5 h. Work-up followed by flash chromatography eluting with ether afforded the product (0.95 g, 72%) as a 3:1 mixture of diastereomers, which crystallised from dichloromethane/hexane as colourless plates, mp 75–82 °C. Found: C, 70.30; H, 8.20; N, 3.70. $C_{21}H_{29}O_4N$ requires: C, 70.20; H, 8.15; N, 3.70%; δ (^{1}H, 500 MHz): 7.14–7.03 (m, 4H, phenyl-H), 4.44 and 4.26 (2×m, 2×1H, OC*H*$_2$), 3.75 and 3.69 (s, 3H, OMe), 3.25 and 3.11 (m, 1H, $CHCO_2Me$), 3.01 (m, 1H, C*H*$_2$CHCO$_2$Me) and 2.88–2.84 (m, 2H, NHC*H* and aliphatic-H), 2.49–2.11 (m, 6H, NH, C*H*$_2$CH$_2$O, C*H*$_2$CHCO$_2$Me and aliphatic-H), 1.93 (m, 1H, aliphatic-H) 1.24 (d, 2×3H, *J* 6.9 Hz, 2×CH_3) and 0.94 and 0.86 (d, 3H, *J* 6.5 Hz, CH_3); δ (^{13}C, 125 MHz): 178.35 and 174.41 (lactone-CO), 146.46 and 146.29 (ester-CO), 137.24 and 136.86, 129.49 and 128.95, and 126.19 and 125.93 (Ar-C), 68.96 and 68.45 (NHCH), 65.53 and 65.33 (spiro-C), 65.13 and 64.82 (CH_2O), 51.72 and 51.56 (CO_2CH_3), 47.33 and 47.17 ($CHCO_2Me$), 41.16 and 40.91, 40.63 and 40.36, 38.26 and 38.12 (C*H*$_2$CHCO$_2$Me, *C*H$_2$CH$_2$O and aliphatic-CH$_2$), 36.25 and 35.68 (aliphatic-CH), 33.55 (aliphatic-CH), 23.94 (2×CH_3), and 17.0 and 16.92 (CH_3); ν_{max} (film): 2959, 1774, 1728, 1508, 1457, 1436, 1374, 1293 and 1170 cm^{-1}; *m*/*z* (%): 359 (M$^+$, 3), 344 (2), 315 (37), 301 (6), 198 (87), 166 (31) and 154 (100).

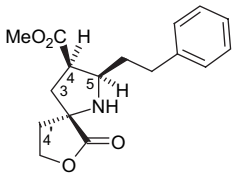
2.3.11. Methyl 2-(2-methyl-4-phenylbutyl)-6-oxo-7-oxa-1-azaspiro[4.4]nonane-3-carboxylate (9k). A mixture of imine **7k** (1.00 g, 3.85 mmol), triethylamine (0.60 mL, 4.2 mmol), silver oxide (0.089 g, 0.38 mmol) and methyl acrylate (0.40 mL, 4.6 mmol) in toluene (40 mL) was stirred for 4 h. Work-up followed by flash chromatography eluting with ether afforded the product (0.91 g, 68%) as a colourless oil, which comprised a 1:1 mixture of diastereomers. Found: C, 69.80; H, 8.00; N, 4.30. $C_{20}H_{27}O_4N$ requires: C, 69.55; H, 7.90; N, 4.05%; δ (^{1}H, 250 MHz): 7.30–7.15 (m, 5H, phenyl-H), 4.37 and 4.20 (2×m, 2×1H, OC*H*$_2$), 3.69 and 3.63 (s, 3H, OMe), 3.39 (m, 1H, NHC*H*), 3.12 (m, 1H, $CHCO_2Me$), 2.64–2.60 (m, 2H, aliphatic-H), 2.40 (dd, 1H, *J* 6.6 and 13.2 Hz, C*H*$_2$CHCO$_2$Me), 2.22–2.15 (m, 3H, NH and C*H*$_2$CH$_2$O), 2.07 (dd, 1H, *J* 8.1 and 13.2 Hz, C*H*$_2$CHCO$_2$Me), 1.67–1.43 (m, 5H, aliphatic-H) and 1.01 and 0.96 (d, 3H, *J* 6.3 Hz, CH_3); ν_{max} (film): 2950, 1773, 1731, 1496, 1455, 1374, 1288, 1213 and 1172 cm^{-1}; *m*/*z* (%): 345 (M$^+$, 3), 314 (3.5), 301 (32), 242 (20), 198 (21), 154 (100) and 91 (12).

2.3.12. Methyl 6-oxo-2-(2-phenylpropyl)-7-oxa-1-azaspiro[4.4]nonane-3-carboxylate (9l). A mixture of imine **7l** (2.16 g, 9.35 mmol), triethylamine (1.40 mL, 10.2 mmol), silver oxide (0.21 g, 0.93 mmol) and methyl acrylate (1.00 mL, 11.2 mmol) in toluene (60 mL) was stirred for 6 h. Work-up followed by flash chromatography eluting with ether separated the 1:1 isomer mixture (combined yield 2.12 g, 71%).

First eluting isomer: Crystallised from ether as colourless plates, mp 90–92 °C. Found: C, 68.00; H, 7.50; N, 4.40. $C_{18}H_{23}O_4N$ requires: C, 68.10; H, 7.30; N, 4.40%; δ (^{1}H, 250 MHz): 7.29–7.18 (m, 5H, phenyl-H), 4.35 and 4.20 (2×m, 2×1H, CH_2O), 3.71 (s, 3H, OMe), 2.98–2.94 (m, 3H, NHC*H*, $CHCO_2Me$ and aliphatic-H), 2.40 (m, 1H, C*H*$_2$CHCO$_2$Me), 2.19–2.02 (m, 4H, NH, C*H*$_2$CHCO$_2$Me and C*H*$_2$CH$_2$O), 1.73–1.63 (m, 2H, aliphatic-H) and 1.27 (d, 3H, *J* 7.0 Hz, CH_3); ν_{max} (film): 2959, 1773, 1730, 1452, 1436, 1373, 1215, 1173, 1109, 1076 and 1021 cm^{-1}; *m*/*z* (%, ES): 318 (M$^+$+1, 100).

Second eluting isomer: Crystallised from ether as colourless plates, mp 83–85 °C. Found: C, 68.10; H, 7.50; N, 4.40. $C_{18}H_{23}O_4N$ requires: C, 68.10; H, 7.30; N, 4.40%; δ (^{1}H, 250 MHz): 7.33–7.19 (m, 5H, phenyl-H), 4.34 and 4.16 (2×m, 2×1H, CH_2O), 3.71 (s, 3H, OMe), 3.20–3.11 (m, 2H, NHC*H* and $CHCO_2Me$), 2.86 (m, 1H, aliphatic-H), 2.42 (dd, 1H, *J* 6.3 and 13.2 Hz, C*H*$_2$CHCO$_2$Me), 2.19 (b, 1H, NH), 2.16–2.02 (m, 3H, C*H*$_2$CHCO$_2$Me and C*H*$_2$CH$_2$O), 1.86 and 1.67 (2×m, 2×1H, aliphatic-H) and 1.25 (d, 3H, *J* 6.9 Hz, CH_3); ν_{max} (film): 2959, 1773, 1730, 1437, 1374, 1214, 1173, 1118, 1078 and 1019 cm^{-1}; *m*/*z* (%, ES): 318 (M$^+$+1, 100).

2.3.13. Methyl 6-oxo-2-(2-phenylethyl)-7-oxa-1-azaspiro-[4.4]nonane-3-carboxylate (9m). A mixture of imine **7m** (1.00 g, 4.6 mmol), triethylamine (0.70 mL, 5.62 mmol), silver oxide (0.11 mg, 0.46 mmol) and methyl acrylate (0.50 mL, 5.5 mmol) in toluene (30 mL) was stirred for 6 h. Work-up followed by flash chromatography eluting with ether afforded the product (1.20 g, 86%), which crystallised from dichloromethane/hexane as colourless plates, mp 63–65 °C. Found: C, 67.05; H, 7.05; N, 4.55. $C_{17}H_{21}O_4N$ requires: C, 67.30; H, 7.00; N, 4.60%; δ (^{1}H, 500 MHz): 7.29–7.25 (m, 2H, phenyl-H), 7.20–7.17 (m, 3H, phenyl-H), 4.39 (ddd, 1H, *J* 3.8, 7.8 and 9.1 Hz, CH_2O), 4.21 (m, 1H, CH_2O), 3.69 (s, 3H, OMe), 3.30 (ddd, 1H, *J* 5.2, 7.6 and 8.8 Hz, NHC*H*), 3.14 (q, 1H, *J* 7.5 Hz, $CHCO_2Me$), 2.81 and 2.67 (2×m, 2×1H, aliphatic-H), 2.46 (dd, 1H, *J* 7.3 and 13.2 Hz, C*H*$_2$CHCO$_2$Me), 2.28–2.21 (m, 2H, NH and C*H*$_2$CH$_2$O), 2.14 (m, 1H, C*H*$_2$CH$_2$O), 2.08 (dd, 1H, *J* 8.0 and 13.2 Hz, C*H*$_2$CHCO$_2$Me) and 1.86–1.74 (m, 2H, aliphatic-H); ν_{max} (film): 2949, 1772, 1729, 1496, 1455, 1436, 1373, 1278, 1214, 1172 and 1074 cm^{-1}; *m*/*z* (%, ES): 304 (M$^+$+1, 100). In the NOE 4′-H proton was overlapped with aliphatic protons.



NOE data for **9m**:

Signal irradiated	Enhancement (%)			
	5-H	4-H	3-H	Aliphatic-H
5-H		6.6	—	4.8
4-H	4.3		5.2	—

2.3.14. Methyl 2-(1-*tert*.-butoxycarbonyl)amino-2-phenylethyl-6-oxo-7-oxa-1-azaspiro[4.4]nonane-3-carboxylate (9n). A mixture of imine **7n** (1.23 g, 3.7 mmol), triethylamine (0.57 mL, 4.0 mmol), silver oxide (0.085 g, 0.37 mmol) and methyl acrylate (0.40 mL, 4.4 mmol) in toluene (30 mL) was stirred for 3 h. Wok-up followed by flash chromatography eluting with ether separated the 1:1 isomer mixture (combined yield 0.72 g, 46%).

First eluting isomer: Crystallised from dichloromethane/hexane as colourless plates, mp 65–67 °C. $[\alpha]_D^{18}$ +10.98 (*c* 1.02, $CHCl_3$). Found: C, 63.20; H, 7.40; N, 6.50. $C_{22}H_{30}O_6N_2$ requires: C, 63.15; H, 7.20; N, 6.70%; δ (^{1}H, 250 MHz): 7.31–7.19 (m, 5H, phenyl-H), 6.04 (d, 1H, *J* 10.3 Hz, amide-NH), 4.38 (m, 1H, CH_2O), 4.21–4.07 (m, 2H, CH_2O and amide NHC*H*), 3.72 (s, 3H, OMe), 3.68 (m, 1H, NHC*H*), 3.20 (m, 1H, $CHCO_2Me$), 2.87–2.55 (m, 3H, CH_2CHCO_2Me and aliphatic-H), 2.24–2.05 (m, 4H, CH_2CH_2O, NH and CH_2CHCO_2Me) and 1.36 (s, 3×H, 3×CH_3); ν_{max} (film): 3346, 2977, 1767, 1733, 1700, 1653, 1558, 1539, 1506, 1496, 1390, 1225 and 1172 cm^{-1}; *m/z* (%): 419 (M^++1, 1.5), 374 (4), 345 (11), 227 (29), 198 (100), 166 (34), 120 (80) and 91 (41).

Second eluting isomer: Crystallised from dichloromethane/hexane as colourless needles, mp 178–180 °C. $[\alpha]_D^{18}$ −13.3 (*c* 0.96, $CHCl_3$). Found: C, 62.90; H, 7.20; N, 6.40. $C_{22}H_{30}O_6N_2$ requires: C, 63.15; H, 7.20; N, 6.70%; δ (^{1}H, 250 MHz): 7.31–7.18 (m, 5H, phenyl-H), 4.50 (d, 1H, *J* 9.2 Hz, amide-NH), 4.43 (ddd, 1H, *J* 4.4, 7.8 and 9.2 Hz, CH_2O), 4.24 (dt, 1H, *J* 6.8 and 9.0 Hz, CH_2O), 3.93 (m, 1H, amide NHC*H*), 3.70 (s, 3H, OMe), 3.40 (m, 1H, NHC*H*), 3.10 (q, 1H, *J* 7.1 Hz, $CHCO_2Me$), 3.01–2.98 (m, 2H, aliphatic-CH_2), 2.50–2.09 (m, 5H, NH, CH_2CHCO_2Me and CH_2CH_2O) and 1.38 (s, 3×H, 3×CH_3); ν_{max} (film): 3371, 2978, 2949, 1775, 1754, 1730, 1700, 1518, 1448, 1430, 1367, 1316 and 1273 cm^{-1}; *m/z* (%): 418 (M^+, <1), 345 (7), 301 (10), 227 (20), 198 (100), 166 (29), 120 (84) and 91 (47).

2.3.15. Methyl 2-[2-(1,3-benzodioxol-5-yl)-1-methylethyl]-6-oxo-7-oxa-1-azaspiro[4.4]nonane-3-carboxylate (9o). A mixture of imine **7o** (1.37 g, 5.0 mmol), triethylamine (0.80 mL, 10.2 mmol), silver oxide (0.12 g, 0.5 mmol) and methyl acrylate (0.56 mL, 6.3 mmol) in toluene (30 mL) was stirred for 4 h. Work-up followed by flash chromatography eluting with ether separated the 3:1 mixture of isomers (combined yield 1.45 g, 80%).

First eluting isomer: Crystallised from dichloromethane/hexane as colourless plates, mp 85–87 °C. Found: C, 63.00; H, 6.45; N, 3.90. $C_{19}H_{23}O_6N$ requires: C, 63.15; H, 6.40; N, 3.90%; δ (^{1}H, 250 MHz): 6.73–6.62 (m, 4H, phenyl-H), 5.92 (s, 2H, OCH_2O), 4.46 (ddd, 1H, *J* 4.7, 7.6 and 9.0 Hz, CH_2O), 4.27 (m, 1H, CH_2O), 3.70 (s, 3H, OMe), 3.09 (m, 1H, $CHCO_2Me$), 2.94 (dd, 1H, *J* 3.5 and 13.4 Hz, CH_2CHCO_2Me), 2.82 (m, 1H, NHC*H*), 2.62–2.08 (m, 6H, NH, CH_2CHCO_2Me, CH_2CH_2O and aliphatic-H), 1.89 (m, 1H, aliphatic-H) and 0.86 (d, 3H, *J* 6.7 Hz, CH_3); ν_{max} (film): 2915, 1774, 1727, 1502, 1489, 1440, 1373, 1294 and 1212 cm^{-1}; *m/z* (%): 361 (M^+, 13), 317 (32), 198 (85), 166 (42), 154 (100), 135 (82) and 94 (41).

Second eluting isomer: Crystallised from dichloromethane/hexane as colourless plates, mp 90–92 °C. Found: C, 62.80; H, 6.35; N, 3.60. $C_{19}H_{23}O_6N$ requires: C, 63.15; H, 6.40; N, 3.90%; δ (^{1}H, 250 MHz): 6.74–6.54 (m, 4H, phenyl-H), 5.93 (s, 2H, OCH_2O), 4.42 (ddd, 1H, *J* 4.1, 7.8 and 9.1 Hz, CH_2O), 4.23 (m, 1H, CH_2O), 3.76 (s, 3H, OMe), 3.24 (ddd, 1H, *J* 4.8, 6.9 and 8.3 Hz, $CHCO_2Me$), 2.99 (m, 1H, NHC*H*), 2.89 (m, 1H, aliphatic-H), 2.44 (dd, 1H, *J* 4.8 and 13.4 Hz, CH_2CHCO_2Me), 2.35–2.10 (m, 4H, CH_2CHCO_2Me, CH_2CH_2O and aliphatic-H), 1.90 (m, 1H, aliphatic-H), 1.68 (b, 1H, NH) and 0.94 (d, 3H, *J* 6.5 Hz, CH_3); ν_{max} (film): 2951, 1772, 1726, 1503, 1489, 1440, 1443 and 1188 cm^{-1}; *m/z* (%): 361 (M^+, 16), 317 (38), 225 (19), 198 (100), 166 (39), 154 (58), 135 (63) and 94 (35).

2.3.16. Methyl 2-(8,8-dimethyl-1,2,3,4,5,6,7,8-octahydro-2-naphthalenyl)-6-oxo-7-thia-1-azaspiro[4.4]nonane-3-carboxylate (10a). A mixture of imine **8a** (1.00 g, 3.4 mmol), DBU (0.50 mL, 3.4 mmol), silver oxide (0.079 g, 0.34 mmol) and methyl acrylate (0.37 mL, 4.0 mmol) in toluene (40 mL) was stirred for 4 h. Work-up followed by flash chromatography eluting with 3:2 v/v ether/hexane afforded the product (0.44 g, 34%) as a colourless gum, which comprised a 1:1 mixture of diastereomers. Found: C, 67.10; H, 8.35; N, 3.50; S, 8.30. $C_{21}H_{31}O_3NS$ requires: C, 66.80; H, 8.30; N, 3.70; S, 8.50%; δ (^{1}H, 250 MHz): 3.68 and 3.67 (s, 3H, OMe), 3.26–3.20 (m, 3H, CH_2S and $CHCO_2Me$), 2.95 (m, 1H, NHC*H*) and 2.30–1.40 (m, 18H, NH, CH_2CHCO_2Me, CH_2CH_2S and aliphatic-H) and 0.95 (s, 2×3H, 2×CH_3); ν_{max} (film): 2926, 1731, 1698, 1436, 1199 and 1168 cm^{-1}; *m/z* (%): 378 (M^++1, 34), 349 (6), 334 (11), 316 (37), 290 (36), 187 (74), 128 (69) and 94 (25).

2.3.17. Methyl 2-[4-(4-methyl-3-pentenyl)-3-cyclohexen-1-yl]-6-oxo-7-thia-1-azaspiro[4.4]nonane-3-carboxylate (10b). A mixture of imine **8b** (1.20 g, 4.1 mmol), DBU (0.62 mL, 4.1 mmol), silver oxide (0.095 g, 0.41 mmol) and methyl acrylate (0.45 mL, 4.9 mmol) in toluene (50 mL) was stirred for 3 h. Work-up followed by flash chromatography eluting with 3:2 v/v ether/hexane afforded the product (1.00 g, 64%) as a pale yellow oil, which comprised a 1:1 mixture of diastereomers. Found: C, 67.00; H, 8.45; N, 3.90; S, 8.30. $C_{21}H_{31}O_3NS$ requires: C, 66.80; H, 8.30; N, 3.70; S, 8.50%; δ (^{1}H, 250 MHz): 5.38 and 5.36 (m, 1H, cyclohexenyl olefinic-H), 5.08 (m, 1H, olefinic-H), 3.69 and 3.68 (s, 3H, OMe), 3.28–2.92 (m, 4H, CH_2S, $CHCO_2Me$ and NHC*H*), 2.27–1.89 (m, 15H, NH, CH_2CH_2S, CH_2CHCO_2Me and aliphatic-H), 1.68 and 1.60 (s, 2×3H, 2×CH_3) and 1.35 (m, 1H, aliphatic-H); ν_{max} (film): 2915,

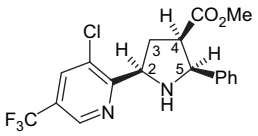
1731, 1697, 1436, 1374, 1272, 1199 and 1168 cm^{-1}; *m/z* (%): 378 (M^++1, 9), 349 (67), 316 (49), 280 (100), 187 (45), 128 (53) and 69 (59).

2.3.18. Methyl 2-[2-(4-isopropylphenyl)-1-methylethyl]-6-oxo-2-phenyl-7-thia-1-azaspiro[4.4]nonane-3-carboxylate (10c). A mixture of imine **8c** (1.57 g, 5.4 mmol), DBU (0.80 mL, 5.42 mmol), silver oxide (0.125 g, 0.54 mmol) and methyl acrylate (0.60 mL, 6.5 mmol) in toluene (60 mL) was stirred for 5 h. Work-up followed by flash chromatography eluting with 2:1 v/v ether/hexane separated the 3:1 mixture of diastereomers (combined yield 1.31 g, 64%).

First eluting isomer: Crystallised from dichloromethane/hexane as a colourless amorphous powder, mp 75–77 °C. Found: C, 67.40; H, 8.05; N, 3.75; S, 8.50. $C_{21}H_{29}O_3NS$ requires: C, 67.15; H, 7.80; N, 3.75; S, 8.55%; δ (^{1}H, 250 MHz): 7.13–7.08 (m, 4H, phenyl-H), 3.67 (s, 3H, OMe), 3.32–3.23 (m, 2H, CH_2S), 3.06–2.89 (m, 2H, $CHCO_2Me$ and aliphatic-H), 2.87–2.82 (m, 2H, NHC*H* and aliphatic-H), 2.48 (dd, 1H, *J* 8.8 and 13.3 Hz, CH_2CHCO$_2$Me), 2.29–2.22 (m, 4H, NH, CH_2CH$_2$S and aliphatic-H), 2.10 (m, 1H, CH_2CHCO$_2$Me), 1.90 (m, 1H, aliphatic-H), 1.24 (d, 2×3H, *J* 6.9 Hz, 2×CH_3) and 0.85 (d, 3H, *J* 6.6 Hz, CH_3); ν_{max} (film): 2958, 1731, 1698, 1436, 1199 and 1170 cm^{-1}; *m/z* (%): 376 (M^++1, <1), 347 (30), 314 (20), 288 (81), 187 (58), 128 (62) and 91 (100).

Second eluting isomer: Pale yellow oil. Found: C, 67.20; H, 7.90; N, 3.45; S, 8.40. $C_{21}H_{29}O_3NS$ requires: C, 67.15; H, 7.80; N, 3.75; S, 8.55%; δ (^{1}H, 250 MHz): 7.27–7.01 (m, 4H, phenyl-H), 3.73 (s, 3H, OMe), 3.28–3.17 (m, 3H, CH_2S, and $CHCO_2Me$), 3.03 (dd, 1H, *J* 6.7 and 8.8 Hz, NHC*H*), 2.95–2.84 (m, 2H, CH_2CHCO$_2$Me and aliphatic-H), 2.32–2.04 (m, 6H, NH, CH_2CH$_2$S, CH_2CHCO$_2$Me and aliphatic-H), 1.93 (m, 1H, aliphatic-H), 1.23 (d, 2×3H, *J* 6.9 Hz, 2×CH_3) and 0.94 (d, 3H, *J* 6.5 Hz, CH_3); *m/z* (%): 376 (M^++1, 1), 347 (68), 314 (37), 288 (100), 214 (25), 187 (61) and 91 (16).

2.3.19. Methyl 5-[2-chloro-4-(trifluoromethyl)phenyl]-2-phenylpyrrolidine-3-carboxylate (17). A mixture of imine **15** (0.30 g, 1.0 mmol), triethylamine (0.15 mL, 1.1 mmol), silver oxide (0.023 g, 0.1 mmol) and methyl acrylate (0.11 mL, 1.2 mmol) in toluene (10 mL) was stirred for 5 h. Work-up followed by flash chromatography eluting with ether afforded the product (0.17 g, 44%), which crystallised from dichloromethane/hexane as colourless plates, mp 145–147 °C. Found: C, 56.00; H, 4.25; N, 7.20; Cl, 9.30. $C_{18}H_{16}O_2N_2ClF_3$ requires: C, 56.20; H, 4.20; N, 7.30; Cl, 9.20%; δ (^{1}H, 500 MHz): 8.83 (d, 1H, *J* 0.9 Hz, pyridyl-H), 7.94 (s, 1H, pyridyl-H), 7.39 and 7.33 (2×m, 2×2H, phenyl-H), 7.28 (m, 1H, phenyl-H), 4.83 (apparent t, 1H, *J* 8.2 Hz, NHC*H*-pyridyl), 4.68 (d, 1H, *J* 8.1 Hz, NHC*H*-phenyl), 3.89 (b, 1H, NH), 3.51 (dt, 1H, *J* 6.6 and 8.1 Hz, $CHCO_2Me$), 3.18 (s, 3H, OMe), 2.71 (m, 1H, CH_2CHCO$_2$Me) and 2.14 (ddd, 1H, *J* 6.6, 9.0 and 13.0 Hz, CH_2CHCO$_2$Me); ν_{max} (film): 1732, 1603, 1456, 1436, 1322, 1200, 1162 and 1134 cm^{-1}; *m/z* (%): 385 (M^+, 0.7), 383 (M^+, 2), 367 (1.5), 365 (4), 300 (32), 298 (100), 284 (31), 282 (90), 223 (13), 221 (41) and 91 (20).



NOE data for **17**:

Signal irradiated	Enhancement (%)				
	5-H	4-H	3-H	2-H	Ar-H
5-H		9.4	—	2.0	8.4
4-H	8.3		5.1	1.2	2.0
2-H	1.6	1.6	4.8		—

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