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Synthesis of 2-azaspiro[4.4]nonan-1-ones via phosphine-catalysed [3+2]-cycloadditions

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Abstract

The phosphine-catalysed [3+2]-cycloaddition of the 2-methylene γ -lactams 4 and 5 and the acrylate 6 with the ylides derived from the ethyl ester, the amide or the chiral camphor sultam derivative of 2-butyric acid (7a-c) give directly, or indirectly after reductive cyclization, spiro-heterocyclic products. The acid 32 underwent Curtius rearrangement and then acid hydrolysis to give two novel spiro-cyclic ketones, 41 and 42.

Keywords

Synthesis, azaspiro, nonan, ones, via, phosphine, catalysed, cycloadditions, CMMB

Disciplines

Life Sciences | Physical Sciences and Mathematics | Social and Behavioral Sciences

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Synthesis of 2-Azaspiro[4.4]nonan-1-ones via Phosphine-catalysed [3+2]-Cycloadditions

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Abstract: The phosphine-catalysed [3+2]-cycloaddition of the 2-methylene γ -lactams **4** and **5** and the acrylate **6** with the ylides derived from the ethyl ester, the amide or the chiral camphor sultam derivative of 2-butyric acid (**7a-c**) give directly, or indirectly after reductive cyclization, spiro-heterocyclic products. The acid **32** underwent Curtius rearrangement and then acid hydrolysis to give two novel spiro-cyclic ketones, **41** and **42**.

Key words: phosphine-catalysed, [3+2]-cycloaddition, 2-methylene γ -lactams, spiro-heterocyclics, Curtius rearrangement.

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1. Introduction

The 2-azaspiro[4.4]nonan-1-one structure (**1**) is found in several bioactive natural products, including alkaloids, where it forms part of a spiro[cyclopentane-1,1'-[1H]isoindol]-3'(2H)-one (**2**) or spiro[3H-indole-3,3'-pyrrolidin]-2(1H)-one (**3**) ring system.^{1,2}

We report here a new strategy for the synthesis of both racemic and enantio-enriched versions of the 2-azaspiro[4.4]nonan-1-one and spiro[cyclopentane-1,1'-[1H]isoindol]-3'(2'H)-one ring systems using the phosphine-catalysed [3+2]-cycloaddition of the ethyl ester (**7a**), the chiral camphor sultam (**7b**) or the amide (**7c**) derivative of 2-butynoic acid with either 2-methylene γ -lactams **4** or **5** or the acrylate **6**, followed by reductive cyclization with zinc (Scheme 1). Enantiomerically enriched versions of **2** can be obtained using or the chiral (1*S*)-camphor sultam analogue **7b** to generate the key spiro-heterocyclic system of these target molecules (Scheme 1). The phosphine-catalysed cycloaddition of ethyl buta-2,3-dienoate or ethyl 2-butynoate with electron-deficient alkenes has been established as a useful method for preparing substituted cyclopenten³⁻¹³ both in racemic and enantio-enriched forms.¹⁴ However, only a few examples of preparing spiro-heterocyclic derivatives using this method have been reported.^{7,11-13} During the initial phase of our study, Lu *et al.* reported the triphenylphosphine-catalysed cycloaddition reaction of **4** and **7a**.¹³

Scheme 1

2. Results and Discussion

The results of the phosphine-catalysed [3+2]-cycloaddition reactions of the 2-methylene γ -lactams **4** and **5** with the ylide **8a** (X = OEt), that was generated *in situ* from the reaction of ethyl 2-butynoate **7a** and tributylphosphine (TBP) are shown in Scheme 2. The reaction of **4**¹³ with ethyl 2-butynoate (2 equiv) and TBP (1 equiv) in benzene solution at RT for 15 h gave a mixture (*ca.* 80 : 20) of two racemic regio-isomeric cycloadducts, **9** and **10**, that were isolated in yields of 51 and 21 %, respectively, after column chromatography. We found that the use of a stoichiometric amount of TBP was required to obtain a good conversion to **9** and **10**. The structures of **9** and **10** were confirmed by extensive 2D NMR experiments and the structure of **10** was established by single-crystal X-ray structural analysis (Figure 1).¹⁵ The spectroscopic data of these compounds agreed well with that reported by Lu *et al.*,¹³ who reported a combined yield for **9** and **10** (d. r. = 62 : 38) of only 33% when the more hindered and less nucleophilic catalyst, triphenylphosphine (0.1 equiv),

was employed. Based on steric considerations alone, the regiochemical outcome of this reaction can be rationalised as occurring *via* the transition state **A** ($R = H$, $X = OEt$) which would be expected to be favoured over the more sterically demanding transition state **B** ($R = H$, $X = OEt$, Scheme 3).^{12,13}

Scheme 2 (compounds **9** and **10** are racemic) **4**; R = H**5**; R = CO_2Et **regioisomer A**

+

regioisomer B**9**; R = H (51%)**11**; R = CO_2Et (28%)**10**; R = H (21%)**[X-ray]****12**; R = CO_2Et **13** (13%)

Scheme 3

Under similar conditions the chiral 2-methylene γ -lactam **5**¹⁶ reacted with the ylide **8a** ($\text{X} = \text{OEt}$) to produce three cycloadducts, **11**, **12** and **13**, in a ratio of 63 : 17 : 30, respectively, from ^1H NMR analysis of the crude reaction mixture (Scheme 2). Diastereomerically pure samples of **11** (28% yield) and **13** (13% yield) could be obtained after extensive purification, however a pure sample of **12** could not be obtained due to difficulties in separating **12** from **11** and **13**. Although the absolute stereochemistries of **11** and **13** could not be unequivocally proven from 2D NMR experiments we assume that the major cycloadduct **11** arises from attack of the ylide onto the face of the 2-methylene group of **5** that is *anti* to the ethyl ester substituent (*via* transition state **A**, $\text{R} = \text{CO}_2\text{Et}$, $\text{X} = \text{OEt}$, Scheme 3).

Figure 1. Molecular projection of **10**.

Treatment of ethyl 2-(2-nitrophenyl)propenoate **6**¹⁷ with ethyl 2-butynoate **7a** and TBP (0.2 equiv) gave the racemic cycloadduct **14** as a single regio-isomer in 93 % yield (Scheme 4). Upon exposure to zinc/aqueous HCl, **14** underwent reductive cyclization to give the spiro[cyclopentane-1,1'-[1H]isoindol]-3'(2'H)-one derivative **15** in 98% yield (Scheme 4).

Scheme 4 (Compounds **14** and **15** are racemic)

In order to prepare enantiomerically enriched versions of **15**, the corresponding cycloaddition reaction of **6** with the chiral alkyne **7b**, derived from Oppolzer's (1*S*)-chiral sultam,¹⁸ was examined (Scheme 5). This reaction produced a 3.3 : 1 mixture of the diastomeric cycloadducts **16** and **17** from which pure samples could be obtained after column chromatography, along with mixed fractions in a combined yield of 66% (Scheme 5). The absolute (1*S*)-configuration of the cyclopentane ring of **16** ($[\alpha]_D^{26} -22.0$ (*c* 0.3, CHCl₃)) was established by a single-crystal X-ray structural analysis (Figure 2)¹⁵ which then allowed assignment of the 1*R*-configuration to this ring of the minor diastereomer **17** ($[\alpha]_D^{24} +19.0$ (*c* 0.6, CHCl₃)). The chiral auxiliary was then removed by methanolysis of (*S*)-**16** and (*R*)-**17** in the presence of samarium(III) triflate¹⁹ to give the methyl esters, (-)-(*S*)-**18** and (+)-(*R*)-**19** in yields of 67% and 68 %, respectively. Reductive cyclization of (-)-(*S*)-**18** or (+)-(*R*)-**19** by treatment with zinc/aqueous HCl gave the tricyclic lactams, (-)-(*S*)-**20** or (+)-(*R*)-**21**, respectively (Scheme 5).

Figure 2. Molecular projection of **16**.

Scheme 5^a

^a *Reagents and conditions*: (a) $\text{Sm}(\text{OTf})_3$ (1 equiv), MeOH , 50°C , 18 h, 67% **(S)-18**, 68% **(R)-19**; (b) Zn dust (24 equiv), 8.9M HCl , $\text{MeOH}/\text{H}_2\text{O}$, reflux, 2 h, 69% **(S)-20**, 56% **(R)-21**.

The spiro-cyclic compounds **9**, **10** and **15** have three functional groups that can be further derivatised to provide compounds with increased structural diversity. For example, the *N*-Boc protecting group in racemic **9** and **10** was readily removed upon exposure to trifluoroacetic acid (TFA) to give compounds **22** and **28**, respectively (Scheme 6). Both compounds gave single crystals for X-ray structural analysis (not shown).¹⁵ The nitrogen atom of **22** and **28** was readily *N*-benzylated with benzyl bromide under basic conditions and the resulting compounds **23** and **29**, respectively, were converted to the *N*-aryl amide derivatives **25a,b**¹⁵ and **31a**, respectively, through amide bond formation between their respective carboxylic acids, **24** and **30**¹⁵ and aniline and 4-dimethylaminoaniline (Scheme 6). Amide **27**¹⁵ was obtained from the coupling reaction of aniline and the carboxylic acid **26** obtained from base catalysed hydrolysis of ester **22**.

Scheme 6^a (all compounds are racemic)

^a *Reagents and conditions:* (a) TFA, DCM, 2.5 h, 91% (**22**), 86% (**28**); (b) NaH (1.3 equiv), Bu₄NI (0.1 equiv), BnBr (1.5 equiv), dry THF, RT, 1-5 h, 74% (**23**), 47% (**29**); (c) K₂CO₃ (2 equiv), MeOH/H₂O, high pressure tube, 60°C, 1d, 93% (**24**), 53% (**26**), 80% (**30**); (d) Aniline or 4-*N,N*-dimethylaminoaniline (1.2 equiv), HOBT (1 equiv), EDCI (1 equiv), dry MeCN, 0°C→60°C, 1-2d, 54% (**25a**), 64% (**25b**), 91% (**27**), 91% (**31a**).

Using related chemistry, the ester **15** was converted to the *N*-aryl amides **33a,b** via the carboxylic acid **32** (Scheme 7).

Scheme 7^a (all compounds are racemic)

^a *Reagents and conditions*: (a) K₂CO₃ (2 equiv), MeOH/H₂O, high pressure tube, 60°C, 5 h, 94%; (b) Aniline or 4-*N,N*-dimethylaminoaniline (1.7 equiv), HOBT (1 equiv), EDCI (1 equiv), MeCN, 0°C→RT, 15 h, 92% (**33a**), 44% (**33b**).

To explore a more direct method to these *N*-aryl amide derivatives, the phosphine-catalysed [3+2]-cycloaddition reactions of the 2-methylene γ -lactam **4** and acrylate **6** with the ylide **8** (X = NHPH), that was generated *in situ* from the reaction of *N*-phenyl 2-butyneamide **34**, was examined (Schemes 8 and 9). These reactions were unsuccessful, presumably due to internal quenching of the ylide **8** (X = NHPH) by the relatively acidic secondary amide NH. In accordance with this hypothesis was the fact that the corresponding *N*-PMB protected ylide **8c** (X = N(PMB)Ph), generated *in situ* from the tertiary amide **7c**, gave the racemic cycloadducts **35** and **36**, in yields of 14% and 55%, respectively (Schemes 8 and 9). These reactions, while poor to modest in yields, were completely regioselective, presumably due to the increased steric bulk of the ylide **8c** which would further destabilize transition state **B** over transition state **A** (Scheme 3). Treatment of the cycloaddition product **35** with TFA, gave *N*-phenyl amide **27** (Scheme 8) that was identical to the compound **27** prepared according to Scheme 6. Similarly, reductive cyclization of **36** followed by deprotection of

the product **37** with TFA gave **33a** (Scheme 9) that was identical to the compound **33a** prepared according to Scheme 7. To the best of our knowledge the phosphine-catalysed [3+2]-cycloaddition reactions of alkenes and 2-butyrimides has not been previously reported.

Scheme 8^a (all compounds are racemic)

^a *Reagents and conditions:* (a) Anisole (10 equiv), TFA (125 equiv), DCM, 15 h, 57%.

Scheme 9^a (all compounds are racemic)

^a *Reagents and conditions:* (a) Activated Zn dust (3.4 equiv), acetic acid, 1.5 h, 16%; (b) Anisole (10 equiv), TFA (125 equiv), DCM, 15 h, 52%.

With the aim of preparing the novel spiro-cyclic ketone **41**, the racemic carboxylic acid **32** was converted to the corresponding acyl azide by treatment with diphenylphosphoryl azide (DPPA),²⁰ which was then heated under Curtius rearrangement conditions. Acid hydrolysis of the resulting product mixture gave *ca* a 1 : 1 mixture of the spiro-cyclic ketones **41** and **42** (Scheme 10). These compounds were readily separated by column chromatography and were isolated in yields of 54% and 35%, respectively. The ¹H NMR spectrum of **42** showed two distinct N-H resonances (δ_{H} (C₆D₆) 7.96 (bs), 4.84 (bs)) and a deshielded aromatic proton (δ_{H} (C₆D₆) 8.64 (d, *J* 8 Hz), consistent with the presence of the *N*-aminocarbonyl group with internal H-bonding to the lactam carbonyl group. The structures of **41** and **42** were confirmed by a single crystal X-ray structural analysis (**42**: Figure 3).¹⁵ We assume that the unexpected product **42** arises from self-condensation of the intermediate vinyl isocyanate **38** to give the carbamate derivative **39**. Acid

hydrolysis of **39** then gives, *via* **40**, the spiro-cyclic ketones **41** and **42** (Scheme 10). We have not however attempted to isolate or characterize the intermediates involved.

Scheme 10 (all compounds are racemic)

Figure 3. Molecular projection of **42**.

Catalytic hydrogenation of the alkene moiety of racemic **15** gave a 1.8 : 1 mixture of the diastereomers **43** and **44**, respectively that were readily separated by column chromatography (Scheme 11). The relative stereochemistry of **43** was determined by 1D NOE experiments that showed a significant enhancement of the signal for the methine proton Ha upon radiation of the aromatic proton Hb and *vice versa*.

Scheme 11 (all compounds are racemic)

3. Cytotoxicity Studies

Compounds **15**, **25a,b**, **27**, **31**, **33a,b**, **41**, **42**, **43** and **44** were all tested for their cytotoxic activity against the cancer cell lines H460 (human non small cell lung), MCF-7 (human breast) and SF-268 (human CNS) at the Peter MacCallum Cancer Centre, St Andrew's Place, East Melbourne, Vic, 3002, Australia. Biological testing was performed using standard NCI procedures at a drug concentration of 25 μ M (5 mM drug stocks were prepared in DMSO. Cells were then exposed to 25 μ M of each drug for 72 h. The cells were then fixed, stained with SRB and the percentage cell

growth relative to the solvent control determined). Percent cell growth calculated from this testing showed little or no cytotoxic activity. The best activity was 50% cell growth at 25 μ M for **33b** against H460.

In conclusion, we have developed a new strategy for the synthesis of both racemic and enantio-enriched versions of the 2-azaspiro[4.4]nonan-1-one and spiro[cyclopentane-1,1'-[1H]isoindol]-3'(2'H)-one ring systems using the phosphine-catalysed [3+2]-cycloaddition of both ester (**7a**) and amide derivatives (**7c**) of 2-butyric acid. Enantiomerically enriched versions of **2** can be obtained using a chiral (1*S*)-camphor sultam derivative **7b** of 2-butyric acid. We have also demonstrated the potential of these compounds as scaffolds for developing libraries of novel spiro-heterocyclic compounds.

4. Experimental

For X-ray structure determinations see supporting information. All ^1H NMR spectra were performed at 300 MHz and all ^{13}C NMR (DEPT) spectra at 75 MHz in CDCl_3 solution, unless otherwise noted. **Abbreviations:** PS (petroleum spirit, bp 40-60°C) and DCM (dichloromethane).

Ethyl (5*S*^{*}) 2-(*tert*-butoxycarbonyl)-1-oxo-2-azaspiro[4.4]non-7-ene-7-carboxylate (9) and Ethyl (5*R*^{*}) 2-(*tert*-butoxycarbonyl)-1-oxo-2-azaspiro[4.4]non-6-ene-6-carboxylate (10)

To a solution of **4** (200.7 mg, 1.02 mmol) in dry benzene (3 mL) was added ethyl 2-butyrate (0.13 mL, 1.12 mmol) and tributylphosphine (0.25 mL, 1.01 mmol). The reaction mixture was allowed to stir at RT for 15 h, under an atmosphere of N_2 . The solvent was then evaporated *in vacuo*. An 82:18 mixture of the two regioisomers, **9** and **10** respectively, resulted (determined from analysis of the ^1H NMR spectrum of the crude reaction product). Compounds **9** and **10** were purified by column chromatography using 10-30% EtOAc:PS as the eluent. These compounds were further purified by PTLC (30% EtOAc:PS). **9**: A yellow oil (161.7 mg, 0.52 mmol, 51%), R_f 0.78 (30% EtOAc:PS). ^1H NMR (C_6D_6 , 500 MHz) δ 6.37 (t, J 2 Hz, 1H, CH=), 3.98 (dd, J 14, 7.5 Hz, 2H, CH_2CH_3), 3.20

(ddd, J 13, 6, 6 Hz, 2H, NCH_2), 3.04 (dq, J 16.5, 2.5 Hz, 1H, CH-6_β), 2.71 (dq, J 18.5, 2.5 Hz, 1H, CH-9_β), 2.13 (d, 16.5 Hz, 1H, CH-6_α), 1.73 (d, 18 Hz, 1H, CH-9_α), 1.48 (s, 9H, $\text{C}(\text{CH}_3)_3$), 1.12 (ddd, J 13, 6, 6 Hz, 1H, $\text{CH}_\text{A}\text{CH}_\text{B-4}$), 1.04 (ddd, J 13, 6, 6 Hz, 1H, $\text{CH}_\text{A}\text{CH}_\text{B-4}$), 0.97 (t, 7.5 Hz, 3H, CH_3CH_2). ^{13}C NMR (C_6D_6 , 75 MHz) δ 175.4 (C-1), 163.7 (CO_2Et), 151.0 (NCO_2), 139.8 (CH=), 134.3 (C-7), 82.1 ($\text{C}(\text{CH}_3)_3$), 60.1 (CH_2CH_3), 51.6 (C-5), 43.3 (CH_2-9), 42.9 (NCH_2), 42.3 (CH_2-6), 33.2 (CH_2-4), 28.1 ($\text{C}(\text{CH}_3)_3$), 14.3 (CH_3CH_2). MS (ES) m/z 348 ($[\text{M}^+ + \text{K}]$, 15%), 332.1 ($[\text{M}^+ + \text{Na}]$, 60%), 310.0 ($[\text{MH}^+]$, 32%), 254.1 ($[\text{MH}^+ - \text{C}(\text{CH}_3)_3]$, 100%), 210.1 ($[\text{MH}^+ - \text{Boc}]$, 85%); HRMS (CI) Calcd for $\text{C}_{16}\text{H}_{24}\text{NO}_5$ $[\text{MH}^+]$ 310.1654. Found: 310.1664. NMR data for **9** agreed well with literature when performed under the literature conditions.¹³ **10**: A white crystalline solid (44.3 mg, 0.14 mmol, 21%), mp. 100-102°C (lit.¹³ 107-110.5°C), R_f 0.58 (30% EtOAc:PS). ^1H NMR (500 MHz) δ 6.99 (t, J 2.5 Hz, 1H, CH=), 4.17 (ddd, J 14.5, 7, 0.5 Hz, 2H, CH_2CH_3), 3.90 (ddd, 10.5, 9.5, 3.5 Hz, 1H, $\text{NCH}_\text{A}\text{CH}_\text{B}$), 3.63 (ddd, J 10.5, 8.5, 8.5 Hz, 1H, $\text{NCH}_\text{B}\text{CH}_\text{A}$), 2.62-2.69 (m, 1H, $\text{CH}_\text{A}\text{CH}_\text{B-8}$), 2.51-2.58 (m, 1H, $\text{CH}_\text{B}\text{CH}_\text{A-8}$), 2.38-2.46 (om, 2H, $\text{CH}_\text{A}\text{CH}_\text{B-9}$ and $\text{CH}_\text{A}\text{CH}_\text{B-4}$), 1.98 (ddd, J 13, 8.5, 4.5 Hz, 1H, $\text{CH}_\text{B}\text{CH}_\text{A-9}$), 1.92 (ddd, J 12.5, 8.5, 4 Hz, 1H, $\text{CH}_\text{B}\text{CH}_\text{A-4}$), 1.54 (s, 9H, $\text{C}(\text{CH}_3)_3$), 1.26 (dt, J 7.5, 2.5 Hz, 3H, CH_3CH_2). ^{13}C NMR δ 176.8 (C-1), 163.6 (CO_2Et), 150.6 (NCO_2), 147.5 (CH=), 138.0 (C-6), 83.0 ($\text{C}(\text{CH}_3)_3$), 60.8 (CH_2CH_3), 59.7 (C-5), 44.2 (NCH_2), 37.4 (CH_2-9), 31.7 (CH_2-8), 29.8 (CH_2-4), 28.4 ($\text{C}(\text{CH}_3)_3$), 14.5 (CH_3CH_2). MS (ES) m/z 310.2 ($[\text{MH}^+]$, 53%), 332.1 ($[\text{M}^+ + \text{Na}^+]$, 29%), 348.1 ($[\text{M}^+ + \text{K}^+]$, 23%), 254.1 ($[\text{MH}^+ - \text{C}(\text{CH}_3)_3]$, 100%), 209.8 ($[\text{MH}^+ - \text{Boc}]$, 95%); HRMS (ES) Calcd for $\text{C}_{16}\text{H}_{24}\text{NO}_5$ $[\text{MH}^+]$ 310.1654. Found: 310.1654. The NMR data collected for **10** agreed well with those found in literature.¹³

2-tert-Butyl 3,7-diethyl (3*S*,5*S*)-1-oxo-2-azaspiro[4.4]non-7-ene-2,3,7-tricarboxylate (11) and 2-tert-butyl 3,7-diethyl (3*S*,5*R*)-1-oxo-2-azaspiro[4.4]non-7-ene-2,3,7-tricarboxylate (13)

To a solution of **5** (125.8 mg, 0.47 mmol) in dry benzene (3 mL) was added ethyl-2-butynoate (0.06 mL, 1.12 mmol) and tributylphosphine (0.25 mL, 1.01 mmol). The reaction was allowed to stir at RT for 15 h, under an atmosphere of N_2 . The solvent was evaporated *in vacuo* and ^1H NMR analysis

showed a mixture of the two diastereomers, **11** and **12**, and one regioisomer **13** (**11:12:13** = 63:17:30). Compounds **11** and **13** were purified by column chromatography using 20-90% EtOAc:PS as eluent and further by PTLC (30% EtOAc:PS). A pure sample of **12** was unable to be isolated. **11**: A yellow oil (50.5 mg, 0.13 mmol, 28%), $[\alpha]_D^{22}$ -17.5 (*c* 4.6, CHCl₃), *R_f* 0.57 (30% EtOAc:PS). ¹H NMR (500 MHz) δ 6.57 (s, 1H, CH=), 4.54 (dd, *J* 9.5, 4.5 Hz, 1H, CH-5), 4.21 (dq, *J* 6.5, 1.5 Hz, 2H, NCHCO₂CH₂), 4.16 (q, *J* 6.7 Hz, 2H, CCO₂CH₂), 3.15 (dd, *J* 16.5, 2 Hz, 1H, CH-6_β), 3.04 (dd, *J* 18.5, 1.5 Hz, 1H, CH-9_β), 2.55 (d, *J* 16.5 Hz, 1H, CH-6_α), 2.39 (d, *J* 17.5 Hz, 1H, CH-9_α), 2.33-2.55 (m, 1H, CH_ACH_B-4), 2.09 (dd, *J* 13, 4 Hz, 1H, CH_BCH_A-4), 1.49 (s, 9H, C(CH₃)₃), 1.23-1.29 (m, 6H, CH₂CH₃). ¹³C NMR δ 176.9 (C-1), 171.5 (NCHCO₂Et), 164.3 (CCO₂Et), 149.6 (NCO₂), 139.8 (CH=), 134.4 (C-7), 84.0 (C(CH₃)₃), 61.9 (NCHCO₂CH₂), 60.7 (CCO₂CH₂), 56.7 (CH-5), 51.0 (C-3), 45.2 (CH₂-9), 43.5 (CH₂-6), 37.9 (CH₂-4), 28.1 (C(CH₃)₃), 14.4 (CH₃CH₂), 14.3 (CH₃CH₂). MS (ES) *m/z* 382.2 ([MH⁺], 5%); HRMS (ES) Calcd for C₁₉H₂₈NO₇ [MH⁺] 382.1866. Found: 382.1892. **13**: A yellow oil (24 mg, 63 μmol, 13%), $[\alpha]_D^{23}$ -1.88 (*c* 0.14, CHCl₃), *R_f* 0.36 (30% EtOAc:PS). ¹H NMR (500 MHz) δ 6.65 (s, 1H, CH=), 4.57 (dd, *J* 9.5, 3.5 Hz, 1H, CH-5), 4.21-4.29 (m, 2H, NCHCO₂CH₂), 4.18 (q, *J* 7.5 Hz, 2H, CCO₂CH₂), 3.12-3.17 (m, 1H, CH-6_β), 3.08-3.12 (m, 1H, CH-9_β), 2.51 (d, *J* 16.5 Hz, 1H, CH-6_α), 2.45 (d, *J* 18.5 Hz, 1H, CH-9_α), 2.33 (dd, *J* 13.5, 9.5 Hz, 1H, CH_ACH_B-4), 2.20 (dd, *J* 13.5, 4 Hz, 1H, CH_BCH_A-4), 1.51 (s, 9H, C(CH₃)₃), 1.31 (t, *J* 7 Hz, 3H, CCO₂CH₂CH₃), 1.27 (t, *J* 7 Hz, 3H, NCHCO₂CH₂CH₃). ¹³C NMR δ 177.0 (C-1), 171.1 (NCHCO₂Et), 164.3 (CCO₂Et), 149.4 (NCO₂), 139.9 (C-8), 133.8 (C-7), 83.8 (C(CH₃)₃), 61.8 (NCHCO₂CH₂), 60.4 (CCO₂CH₂), 56.4 (CH-5), 50.7 (C-3), 44.8 (CH₂-9), 43.6 (CH₂-6), 37.8 (CH₂-4), 27.8 (C(CH₃)₃), 14.2 (CH₃CH₂), 14.1 (CH₃CH₂). MS (ES) *m/z* 382.2 ([MH⁺], 5%); HRMS (ES) Calcd for C₁₉H₂₈NO₇ [MH⁺] 382.1866. Found: 382.1914.

3-Ethyl, 1-methyl 1-(2-Nitrophenyl)-cyclopent-3-ene-1,3-dicarboxylate (**14**)

To a solution of alkene **6** (1.013 g, 4.9 mmol) and ethyl 2-butynoate (0.63 mL, 5.4 mmol) in dry benzene (35 mL) was slowly added tributylphosphine (0.24 mL, 0.98 mmol). The reaction was left to stir for 6 h. Upon evaporation *in vacuo* of volatiles, the resulting crude product was purified by column chromatography using 20-50% EtOAc:PS as eluent to yield a peach coloured oil (1.45 g, 4.5 mmol, 93%), R_f 0.81 (50% EtOAc:PS). ^1H NMR δ 7.93 (dd, J 8.1, 1.5 Hz, 1H, ArH-3), 7.58 (dt, J 7.8, 1.8 Hz, 1H, ArH-5), 7.42 (dt, J 7.6, 1.5 Hz, 1H, ArH-4), 7.40 (d, 7.8 Hz, 1H, ArH-6), 6.74 (t, J 1.8 Hz, 1H, CH=), 4.20 (q, J 6.9 Hz, 2H, CH₂CH₃), 3.64 (s, 3H, CO₂CH₃), 3.62 (dq, J 19.2, 2.7 Hz, 1H, CH-5 α), 3.52 (dq, J 17.4, 2.5 Hz, 1H, CH-2 α), 3.21 (dm, J 17.1 Hz, 1H, CH-2 β), 2.99 (dt, J 19.2, 2.4 Hz, 1H, CH-5 β), 1.29 (t, J 6.9 Hz, 3H, CH₃CH₂). ^{13}C NMR δ 174.0 (C=O₂Me), 164.0 (C=O₂Et), 148.1 (ArC-2), 140.1 (CH=), 138.1 (ArC-1), 133.8 (C-3 $\prime$), 133.2 (ArCH-5), 128.3 (ArCH-6), 128.0 (ArCH-4), 125.3 (ArCH-3), 60.6 (CH₂CH₃), 55.6 (C-1 $\prime$), 52.4 (CO₂CH₃), 45.8 (CH₂-5 $\prime$), 44.2 (CH₂-2 $\prime$), 14.2 (CH₃CH₂). MS (CI) m/z C₁₆H₁₈NO₆ 320 ([MH⁺], 100%), 288 ([MH⁺ - Et], 41%), 206 (68%), 246 (22%), 188 (21%); HRMS (CI) Calcd for C₁₆H₁₈NO₆ [MH⁺] 320.1134. Found: 320.1132.

Ethyl 2-oxo-spiro[3 $\prime$ -cyclopentene-1 $\prime$,3-[3H]indole]-3 $\prime$ -carboxylate (15**)**

To a solution of **14** (29.5 mg, 0.092 mmol) in EtOH (0.7 mL) and H₂O (0.18 mL) was added activated Zn dust (96 mg, 1.5 mmol) and 8.9M HCl (0.14 mL). The reaction was heated at reflux for 2 h. Another portion of activated Zn dust (96 mg, 1.5 mmol) was added and the reaction was left at reflux for an additional 4 h. The mixture was then filtered through celite and diluted with H₂O. The filtrate was then extracted with EtOAc and the organic extracts were combined and dried over MgSO₄ to yield a creamy brown oil (23.4 mg, 0.091 mmol, 98%), R_f 0.5 (50% EtOAc:PS). ^1H NMR (500 MHz) δ 9.15 (bs, 1H, NH), 7.21 (d, J 7.5 Hz, 1H, ArH-4), 7.20 (t, J 8 Hz, 1H, ArH-6), 7.01 (t, J 7.7 Hz, 1H, ArH-5), 6.93 (d, J 8 Hz, 1H, ArH-7), 6.86 (bs, 1H, CH=), 4.23 (q, J 7 Hz, 2H, CH₂CH₃), 3.27 (dd, J 16.5, 2.5 Hz, 1H, CH-2 α), 3.19 (dd, J 18.7, 2.25 Hz, 1H, CH-5 α), 2.90 (d, J 16.5 Hz, 1H, CH-2 β), 2.80 (d, J 18.5 Hz, 1H, CH-5 β), 1.31 (t, J 7.25 Hz, 3H, CH₃CH₂). ^{13}C NMR

δ 183.2 (C-2), 164.2 ($\text{C}=\text{O}_2\text{Et}$), 140.6 ($\text{CH}=\text{}$), 139.7 (C-7a), 136.6 (C-3a), 134.8 (C-3'), 128.1 ($\text{ArCH}=\text{}$), 123.0 ($\text{ArCH}=\text{}$), 122.1 ($\text{ArCH}=\text{}$), 109.9 ($\text{ArCH}=\text{}$), 60.5 (CH_2CH_3), 52.5 (C-3), 44.9 ($\text{CH}_2\text{-}5'$), 43.4 ($\text{CH}_2\text{-}2'$), 14.2 (CH_3CH_2). MS (CI) m/z 258 ($[\text{MH}^+]$, 100%), 212 ($[\text{M}^+-\text{OEt}]$, 12%), 184 ($[\text{M}^+-\text{CO}_2\text{Et}]$, 12%); HRMS (EI) Calcd for $\text{C}_{15}\text{H}_{15}\text{NO}_3$ $[\text{M}^+]$ 257.1052. Found: 257.1048.

(3a*S*,6*R*,7a*R*,4'*S*)-Hexahydro-4'-methoxycarbonyl-4'-(2''-nitrophenyl)-1'-(cyclopenten-1'-ylcarbonyl)-8,8-dimethyl-2,2-dioxide-3*H*-3a,6-methano-2,1-benzisothiazole ((*S*)-16) and **(3a*S*,6*R*,7a*R*,4'*R*)-Hexahydro-4'-methoxycarbonyl-4'-(2''-nitrophenyl)-1'-(cyclopenten-1'-ylcarbonyl)-8,8-dimethyl-2,2-dioxide-3*H*-3a,6-methano-2,1-benzisothiazole ((*R*)-17)**

To a solution of **6** (147 mg, 0.709 mmol) and **7b** (198 mg, 0.706 mmol) in dry benzene (1.5 mL) under a N_2 atmosphere was added tributylphosphine (0.02 mL, 71 μmol). The reaction was stirred at RT for 18 h and then the solvent was removed *in vacuo*. The diastereomeric products were obtained in a ratio of 3.3:1 ((*S*)-16):(*R*)-17) from ^1H NMR analysis of the crude reaction mixture. The crude mixture was purified by column chromatography using 15% EtOAc:PS as eluent, yielding pure diastereomeric products (*S*)-16 (140.6 mg, 0.29 mmol, 13%) and (*R*)-17 (154 mg, 0.32 mmol, 15%) and a mixture (400 mg, 0.82 mmol, 38%) containing both diastereomeric products in a ratio of 4.3:1 ((*S*)-16):(*R*)-17). Further purification by PTLC (20% EtOAc:PS) could yield the pure diastereomeric products. (*S*)-16: A colourless crystal, mp. 196-200 $^\circ\text{C}$, $[\alpha]_{\text{D}}^{26}$ -22.0 (*c* 0.3, CHCl_3), R_f 0.53 (30% EtOAc:PS). ^1H NMR (500 MHz) δ 7.94 (d, *J* 7.5 Hz, 1H, $\text{ArH-}3''$), 7.56 (bs, 2H, $\text{ArH-}5''$, $\text{ArH-}6''$), 7.41 (bs, 1H, $\text{ArH-}4''$), 6.74 (bs, 1H, $\text{CH}=\text{}$), 4.07 (t, *J* 5.5 Hz, 1H, $\text{CH-}7a$), 3.74 (d, *J* 19.5 Hz, 1H, $\text{CH-}3'_\alpha$), 3.66 (s, 3H, CO_2CH_3), 3.64 (d, *J* 19.0 Hz, 1H, $\text{CH-}5'_\alpha$), 3.45 (ABq, *J* 13.5 Hz, 2H, $\text{CH}_2\text{-}3$), 3.19 (d, *J* 19.0 Hz, 1H, $\text{CH-}5'_\beta$), 3.06 (d, *J* 19.5 Hz, 1H, $\text{CH-}3'_\beta$), 2.09-1.99 (m, 2H, $\text{H-}7_\alpha$, $\text{CH-}7_\beta$), 1.97-1.91 (m, 3H, $\text{CH-}4_\beta$, $\text{CH-}5_\beta$, $\text{CH-}6$), 1.44-1.37 (m, 2H, $\text{CH-}4_\alpha$, $\text{CH-}5_\alpha$), 1.24 (s, 3H, $\text{CH}_3\text{-}9$), 1.00 (s, 3H, $\text{CH}_3\text{-}10$). ^{13}C NMR (125 MHz) δ 174.8 ($\text{C}=\text{O}_2\text{Me}$), 171.3 ($\text{C}=\text{CO}$), 148.5 ($\text{ArC-}2''$), 141.6 ($\text{CH}=\text{}$), 138.4 ($\text{ArC-}1''$), 134.7 (C-1'), 133.4 ($\text{ArCH-}5''$), 129.2 ($\text{ArCH-}6''$), 128.0 ($\text{ArCH-}4''$), 125.1 ($\text{ArCH-}3''$), 65.6 ($\text{CH-}7a$), 54.6 (C-4'), 53.7 ($\text{CH}_2\text{-}3$), 52.4 (CO_2CH_3), 48.1

(C-3a), 47.7 (C-8), 47.0 ($\underline{\text{CH}}_2\text{-3}'$), 45.5 ($\underline{\text{CH}}_2\text{-5}'$), 45.2 ($\underline{\text{CH}}\text{-6}$), 38.3 ($\underline{\text{CH}}_2\text{-7}$), 33.3 ($\underline{\text{CH}}_2\text{-4}$), 26.5 ($\underline{\text{CH}}_2\text{-5}$), 21.3 ($\underline{\text{CH}}_3\text{-9}$), 19.9 ($\underline{\text{CH}}_3\text{-10}$). LRMS (EI) m/z 488 ($[\text{M}^+]$, 5%); HRMS (CI) Calcd for $\text{C}_{24}\text{H}_{29}\text{N}_2\text{O}_7\text{S}$ $[\text{MH}^+]$ 489.1695. Found: 489.1690. **(R)-17**: A colourless crystal, mp. 198-202 °C, $[\alpha]_{\text{D}}^{24} +19.0$ (c 0.6, CHCl_3), R_f 0.43 (30% EtOAc:PS). ^1H NMR (500 MHz) δ 7.95 (d, J 8.0 Hz, 1H, $\text{ArH-3}''$), 7.60 (t, 7.5 Hz, 1H, $\text{ArH-5}''$), 7.54 (d, J 8.0 Hz, 1H, $\text{ArH-6}''$), 7.43 (t, 7.5 Hz, 1H, $\text{ArH-4}''$), 6.66 (s, 1H, $\underline{\text{CH}}=$), 4.07 (m, 1H, $\underline{\text{CH}}\text{-7a}$), 3.80 (d, J 19.0 Hz, 1H, $\underline{\text{CH}}\text{-3}'_{\beta}$), 3.68 (s, 3H, $\text{CO}_2\underline{\text{CH}}_3$), 3.50 (d, J 13.5 Hz, 1H, $\underline{\text{CH}}\text{-3}_A$), 3.46-3.42 (m, 3H, $\underline{\text{CH}}\text{-5}'_{\beta}$, $\underline{\text{CH}}\text{-5}'_{\alpha}$, $\underline{\text{CH}}\text{-3}_B$), 2.97 (d, J 19.0 Hz, 1H, $\underline{\text{CH}}\text{-3}'_{\alpha}$), 2.06-2.00 (m, 2H, $\underline{\text{CH}}\text{-7}_{\alpha}$, $\underline{\text{CH}}\text{-7}_{\beta}$), 1.98-1.90 (m, 3H, $\underline{\text{CH}}\text{-4}_{\beta}$, $\underline{\text{CH}}\text{-5}_{\beta}$, $\underline{\text{CH}}\text{-6}$), 1.42 (m, 2H, $\underline{\text{CH}}\text{-4}_{\alpha}$, $\underline{\text{CH}}\text{-5}_{\alpha}$), 1.23 (s, 3H, $\underline{\text{CH}}_3\text{-9}$), 1.00 (s, 3H, $\underline{\text{CH}}_3\text{-10}$). ^{13}C NMR (125 MHz) δ 173.9 (CO_2Me), 165.7 ($=\text{CCO}$), 148.2 ($\text{ArC-2}''$), 139.9 ($\underline{\text{CH}}=$), 138.1 ($\text{ArC-1}''$), 134.7 (C-1'), 133.3 ($\text{ArCH-5}''$), 128.6 ($\text{ArCH-6}''$), 128.0 ($\text{ArCH-4}''$), 125.4 ($\text{ArCH-3}''$), 65.5 ($\underline{\text{CH}}\text{-7a}$), 55.9 (C-4'), 53.6 ($\underline{\text{CH}}_2\text{-3}$), 52.5 ($\text{CO}_2\underline{\text{CH}}_3$), 48.1 (C-3a), 47.7 (C-8), 46.3 ($\underline{\text{CH}}_2\text{-3}'$), 44.8 ($\underline{\text{CH}}_2\text{-5}'$), 45.2 ($\underline{\text{CH}}\text{-6}$), 38.4 ($\underline{\text{CH}}_2\text{-7}$), 33.2 ($\underline{\text{CH}}_2\text{-4}$), 26.5 ($\underline{\text{CH}}_2\text{-5}$), 21.3 ($\underline{\text{CH}}_3\text{-9}$), 19.9 ($\underline{\text{CH}}_3\text{-10}$). MS (EI) m/z 488 ($[\text{M}^+]$, 2.6%); HRMS (CI) Calcd for $\text{C}_{24}\text{H}_{29}\text{N}_2\text{O}_7\text{S}$ $[\text{MH}^+]$ 489.1695. Found: 489.1713.

Dimethyl (1S)-1-(2'-nitrophenyl)-3-cyclopentene-1,3-dicarboxylate ((S)-18)

To a solution of **(S)-16** (199 mg, 0.4 mmol) in dry MeOH (10.2 mL) was added $\text{Sm}(\text{OTf})_3$ (258 mg, 0.43 mmol). The reaction was heated at 50 °C for 15 h. The mixture was then cooled and the solvent was removed *in vacuo*. The residue was then diluted with DCM. The mixture was then washed with brine and sat. NaHCO_3 , dried and solvent removed *in vacuo*. The crude mixture was purified by column chromatography using 8:11:1 (DCM:PS:EtOAc) as eluent to afford **(S)-18** as a peach oil (82.4 mg, 0.27 mmol, 67%) and the recovered chiral auxiliary as white crystals. **(S)-18**: $[\alpha]_{\text{D}}^{24} -42.5$ (c 0.1, CHCl_3), R_f 0.42 (20% EtOAc:PS). ^1H NMR δ 7.95 (dd, J 7.8, 1.5 Hz, 1H, $\text{ArH-3}'$), 7.59 (dt, J 7.5, 1.5 Hz, 1H, $\text{ArH-5}'$), 7.44 (dt, J 7.5, 1.5 Hz, 1H, $\text{ArH-4}'$), 7.42 (dd, J 7.8, 1.5 Hz, 1H, $\text{ArH-6}'$), 6.76 (m, 1H, $\underline{\text{CH}}=$), 3.77 (s, 3H, $=\text{CCO}_2\underline{\text{CH}}_3$), 3.67 (s, 3H, $\text{PhCCO}_2\underline{\text{CH}}_3$), 3.62 (dddd, J 19.5,

5.1, 5.1, 2.7 Hz, 1H, $\underline{\text{CH}}\text{-5}_\alpha$), 3.51 (dddd, J 17.4, 5.1, 5.1, 2.4 Hz 1H, $\underline{\text{CH}}\text{-2}_\alpha$), 3.22 (dt, J 17.1, 1.5 Hz, 1H, $\underline{\text{CH}}\text{-2}_\beta$), 2.98 (dddd, J 19.1, 2.4, 2.4, 0.9 Hz, 1H, $\underline{\text{CH}}\text{-5}_\beta$). ^{13}C NMR (125 MHz) δ 174.0 (PhCCO₂Me), 164.4 (=CCO₂Me), 148.2 (ArC-2'), 140.4 ($\underline{\text{CH}}\text{=}$), 138.0 (ArC-1'), 133.6 (C-3), 133.2 (ArCH-5'), 128.3 (ArCH-6'), 128.1 (ArCH-4'), 125.3 (ArCH-3'), 55.7 (C-1), 52.4 (PhCCO₂CH₃), 51.7 (=CCO₂CH₃), 45.8 ($\underline{\text{CH}}\text{-5}$), 44.2 ($\underline{\text{CH}}\text{-2}$). MS (ES) m/z 306 ($[\text{MH}^+]$, 13%); HRMS (ES) Calcd for C₁₅H₁₆NO₆ $[\text{MH}^+]$ 306.0978. Found: 306.0966.

Dimethyl (1*R*)-1-(2'-nitrophenyl)-3-cyclopentene-1,3-dicarboxylate ((*R*)-19)

The title compound was prepared using a similar method to that described above for the synthesis of (*S*)-18 using (*R*)-17 (81.9 mg, 0.17 mmol). Purification by column chromatography in solvent system 8:11:1 (DCM:PS:EtOAc) gave (*R*)-19 as a brown oil (34.7 mg, 0.1 mmol, 68%) and recovered chiral auxiliary as white crystals. (*R*)-19: $[\alpha]_{\text{D}}^{26} +50.0$ (c 0.7, CHCl₃), R_f = 0.26 in 20% EtOAc:PS). MS (ES+ve) m/z 306 (26%) $[\text{MH}^+]$; HRMS (ES+ve) Calcd for C₁₅H₁₆NO₆ $[\text{MH}^+]$ 306.0978. Found: 306.0984. The ^1H NMR spectrum of (*R*)-19 was identical to that of its enantiomer (*S*)-18.

Methyl (1'*S*)-2-Oxo-spiro[3'-cyclopentene-1',3-[3*H*]indole]-3'-carboxylate (*S*)-20

To a solution of (*S*)-18 (21.7 mg, 0.07 mmol) in MeOH (0.5 mL) and H₂O (0.17 mL) was added activated Zn dust (112 mg, 1.7 mmol) and 8.9 M HCl (0.1 mL). The reaction was heated at reflux for 2 h. The mixture was then cooled and filtered through celite, washing precipitate with H₂O and MeOH. The filtrate was evaporated *in vacuo*. The crude product was purified by column chromatography using 30% EtOAc:PS as eluent and further purified by PTLC (30% EtOAc:PS). (*S*)-20 was obtained as a yellow oil (11.9 mg, 0.049 mmol, 69%), $[\alpha]_{\text{D}}^{24} -40.8$ (c 1.2, CHCl₃), R_f 0.23 (30% EtOAc:PS). ^1H NMR δ 8.73 (bs, 1H, $\underline{\text{NH}}$), 7.21 (dd, J 7.5, 1.2 Hz, 1H, ArH-4), 7.20 (td, J 7.8, 1.2 Hz, 1H, ArH-6), 7.01 (td, J 7.8, 0.9 Hz, 1H, ArH-5), 6.92 (d, J 7.8 Hz, 1H, ArH-7), 6.88-6.84 (m, 1H, $\underline{\text{CH}}\text{-4'}$), 3.79 (s, 3H, $\underline{\text{CH}}\text{-3}$), 3.26 (ddd, J 18.3, 5.1, 2.7, 2.4 Hz, 1H, $\underline{\text{CH}}\text{-2'}$), 3.20 (ddd,

J 20.3, 5.1, 2.7, 2.4 Hz, 1H, $\text{CH-5}'_{\alpha}$), 2.90 (ddd, J 18.3, 2.4, 1.5 Hz, 1H, $\text{CH-2}'_{\beta}$), 2.80 (m, 1H, $\text{CH-5}'_{\beta}$). ^{13}C NMR δ 182.9 (C-2), 164.6 (CO_2Me), 140.9 (CH=), 139.7 (C-7a), 136.5 (C-3a), 134.5 (C-3'), 128.1 (Ar CH-6), 123.0 (Ar CH-5), 122.2 (Ar CH-4), 109.8 (Ar CH-7), 52.5 (C-3), 51.7 (CH_3), 45.0 ($\text{CH}_2\text{-5}'$), 43.4 ($\text{CH}_2\text{-2}'$). MS (EI) m/z 243 ($[\text{M}^+]$, 11%); HRMS (ES) Calcd for $\text{C}_{14}\text{H}_{14}\text{NO}_3$ $[\text{MH}^+]$ 244.0974. Found: 244.0966.

Methyl (1'*R*)-2-Oxo-spiro[3'-cyclopentene-1',3-[3*H*]indole]-3'-carboxylate ((*R*)-21)

The title compound was prepared using a similar method to that described above for the synthesis of (*S*)-**20** using (*R*)-**19** (14.6 mg, 0.048 mmol). (*R*)-**21** was obtained as a peach oil (6.5 mg, 0.027 mmol, 56%), $[\alpha]_{\text{D}}^{23} +57.4$ (c 1.0, CHCl_3), R_f 0.52 (30% EtOAc:PS). The ^1H NMR spectrum of (*R*)-**21** was identical to that of (*S*)-**20**. MS (EI) m/z 243 ($[\text{M}^+]$, 50%); HRMS (ES) Calcd for $\text{C}_{14}\text{H}_{14}\text{NO}_3$ $[\text{MH}^+]$ 244.0974. Found: 244.0963.

Ethyl (5*S*^{*})-1-oxo-2-azaspiro[4.4]non-7-ene-7-carboxylate (22)

To a solution of **9** (852.4 mg, 2.76 mmol) in dry DCM (2.5 mL), was added TFA (2.5 mL). The solution was left to stir for 2.5 h under an atmosphere of N_2 . The solvent was removed *in vacuo*, and the oily residue was then treated with saturated NaHCO_3 solution (2×10 mL) and extracted with DCM (2×20 mL). The organic portions were dried, and evaporated *in vacuo* to yield **22** as brown needle-like crystals (524.2 mg, 2.5 mmol, 91%), mp. 70-78 °C, R_f 0.26 (70% EtOAc:PS). ^1H NMR δ 7.50 (bs, 1H, NH), 6.69 (t, J 2.7 Hz, 1H, CH=), 4.19 (q, J 7.2 Hz, 2H, CH_2CH_3), 3.35 (t, J 7.1 Hz, 2H, NCH_2), 3.02 (od, J 16.5, 2H, CH-6_{β} , CH-9_{β}), 2.59 (d, J 15.9 Hz, 1H, CH-6_{α}), 2.46 (d, J 18.9 Hz, 1H, CH-9_{α}), 2.14-2.16 (m, 2H, $\text{CH}_2\text{-4}$), 1.32 (t, J 7.0 3H, CH_2CH_3). ^{13}C NMR δ 182.35 (C-1), 164.65 (CO_2Et), 140.9 (CH=), 134.5 (C-7), 60.4 (CH_2CH_3), 49.4 (C-5), 43.5 ($\text{CH}_2\text{-9}$), 42.0 ($\text{CH}_2\text{-6}$), 39.5 (NCH_2), 37.8 ($\text{CH}_2\text{-4}$), 14.4 (CH_2CH_3). MS (CI) m/z 210 ($[\text{MH}^+]$, 100%); HRMS (CI) Calcd for $\text{C}_{11}\text{H}_{16}\text{NO}_3$ $[\text{MH}^+]$ 210.1130. Found: 210.1132.

Ethyl (5*S*^{*})-2-benzyl-1-oxo-2-azaspiro[4.4]non-7-ene-7-carboxylate (23)

To a stirred solution of **22** (255.7 mg, 1.22 mmol) in dry THF (15 mL), under an atmosphere of N₂, was added in quick succession, NaH (76 mg, 1.6 mmol, 50% dispersion in paraffin oil), tetrabutylammonium iodide (45 mg, 0.12 mmol) and benzyl bromide (0.22 mL, 1.85 mmol). The reaction mixture was left stirring for 1 h. The reaction mixture was then quenched with H₂O (50 mL) and extracted with DCM (3 × 40 mL). The combined organic extracts were then dried and evaporated *in vacuo*. The crude product was purified by column chromatography using 40-60% EtOAc:PS as the eluent to give **23** as a brown oil (271.5 mg, 0.91 mmol, 74%), R_f 0.56 (50% EtOAc:PS). ¹H NMR δ 7.21-7.34 (m, 5H, ArH), 6.69 (s, 1H, CH=), 4.46 (ABq, *J* 14.5 Hz, 2H, NCH_ACH_BPh), 4.19 (dq, *J* 6.9, 2.4 Hz, 2H, CH₂CH₃), 3.16-3.21 (m, 2H, CH₂-3), 3.05 (od, *J* 16.2 Hz, 2H, CH-6_β, CH-9_β), 2.56 (d, *J* 15.3 Hz, 1H, CH-6_α), 2.43 (d, *J* 18.9 Hz, 1H, CH-9_α), 1.91-2.04 (m, 2H, CH₂-4), 1.28 (dt, *J* 2.4, 7.2 Hz, 3H, CH₂CH₃). ¹³C NMR δ 178.0 (C-1), 164.6 (CO₂Et), 141.0 (CH=), 136.6 (C-7), 134.4 (ArC-*i*), 128.9 (ArCH-*m*), 128.2 (ArCH-*o*), 127.8 (ArC-*p*), 60.5 (CH₂CH₃), 50.3 (C-5), 47.1 (NCH₂Ph), 43.81 (CH₂-9), 43.78 (CH₂-3), 42.2 (CH₂-6), 35.5 (CH₂-4), 14.5 (CH₂CH₃). MS (CI) *m/z* 300 ([MH⁺], 8%); HRMS (EI) Calcd for C₁₈H₂₁NO₃ [M⁺] 299.1521. Found: 299.1508.

(5*S*^{*})-2-Benzyl-1-oxo-2-azaspiro[4.4]non-7-ene-7-carboxylic acid (24)

A solution of a **23** (271.5 mg, 0.91 mmol) in MeOH (2 mL) contained within a sealed tube was added a solution of K₂CO₃ (251 mg, 1.82 mmol) in water (2.5 mL). The mixture was left stirring at 40°C for 4d, another equivalent of K₂CO₃ was added and temperature was raised to 60°C for 1d. The solvent was removed *in vacuo* and the oily residue was dissolved in H₂O (15 mL) and washed with Et₂O (2 × 25 mL). The aqueous fraction was acidified (pH ~ 1) with 10% HCl and extracted with EtOAc (3 × 25 mL). The organic portions were combined, dried and evaporated *in vacuo* to yield a white solid (229.7 mg, 0.85 mmol, 93 %), R_f 0.06 (50% EtOAc:PS). ¹H NMR δ 9.16 (bs, 1H, OH); 7.24-7.35 (m, 3H, ArH), 7.22 (d, *J* 6.3 Hz, 2H, ArH-*o*), 6.81 (s, 1H, CH=), 4.49 (ABq, *J*

14.7 Hz, 2H, $\text{NCH}_A\text{CH}_B\text{Ph}$), 3.17-3.23 (m, 2H, CH_2 -3), 3.11 (ddd, J 18.3, 4.9, 2.2 Hz, 1H, CH -9 β), 3.05 (d, J 16.5, 4.9, 2.2, 1H, CH -6 β), 2.56 (d, J 17.1 Hz, 1H, CH -6 α), 2.45 (d, J 18.6 Hz, 1H, CH -9 α), 1.92-2.08 (m, 2H, CH_2 -4). ^{13}C NMR δ 178.1 (C-1), 168.8 (CO_2H), 143.5 ($\text{CH}=\text{}$), 136.4 (C-7), 133.9 ($\text{ArC}-i$), 128.9 ($\text{ArCH}-m$), 128.2 ($\text{ArCH}-o$), 127.8 ($\text{ArCH}-p$), 50.7 (C-5), 47.4 (NCH_2Ph), 44.1 (CH_2 -9), 44.0 (CH_2 -3), 42.0 (CH_2 -6), 35.6 (CH_2 -4). MS (CI) m/z 272 ($[\text{MH}^+]$, 100%); HRMS (CI) Calcd for $\text{C}_{16}\text{H}_{17}\text{NO}_3$ [M^+] 271.1208. Found: 271.1123.

(5*S*^{*})-2-Benzyl-1-oxo-*N*-phenyl-2-azaspiro[4.4]non-7-ene-7-carboxamide (25a)

To a solution of **24** (52.2 mg, 0.21 mmol) and HOBT (26 mg, 0.2 mmol) in dry MeCN (2 mL) at 0°C, was added aniline (0.02 mL, 0.25 mmol). The solution was stirred for 10 min at 0°C before the addition of EDCI (38.2 mg, 0.2 mmol) and left to stir at RT for 15 h and then at 60°C for 2 h. The solvent was then removed, and the residue was extracted with DCM and washed successively with H_2O and brine. The organic portions was then dried and evaporated *in vacuo*. Purification of the crude product was achieved through column chromatography using 70% EtOAc:PS as the eluent to yield **25a** as white crystals (36.2 mg, 0.11 mmol, 54%), mp. 148-150°C, R_f 0.32 (60% EtOAc:PS). ^1H NMR (500 MHz) δ 7.55 (d, J 8 Hz, 2H, $\text{ArH}-o$), 7.29-7.34 (m, 5H, ArH), 7.23 (d, J 7.5 Hz, 2H, $\text{ArH}-m$), 7.11 (t, J 7.25 Hz, 1H, $\text{ArH}-p$), 6.50 (s, 1H, $\text{CH}=\text{}$), 4.49 (ABq, J 14.5 Hz, 2H, NCH_2), 3.21 (q, J 7 Hz, 2H, CH_2 -3), 3.15 (d, J 16 Hz, 1H, CH -6 β), 3.08 (d, J 18 Hz, 1H, CH -9 β), 2.68 (d, J 15 Hz, 1H, CH -6 α), 2.49 (d, 18 Hz, 1H, CH -9 α), 2.00-2.11 (m, 2H, CH_2 -4). ^{13}C NMR (125 MHz) δ 177.6 (C-1), 162.7 (CONHPh), 137.8 ($\text{ArC}-i$), 137.7 (C-7), 136.2 ($\text{ArC}-i'$), 135.0 ($\text{CH}=\text{}$), 128.8 (ArCH), 128.6 ($\text{ArCH}-m$), 127.9 (ArCH), 127.5 (ArCH), 124.2 ($\text{ArCH}-p$), 119.9 ($\text{ArCH}-o$), 50.3 (C-5), 47.1 (NCH_2), 43.7 (CH_2 -3 and CH_2 -9), 42.4 (CH_2 -6), 35.3 (CH_2 -4). MS (CI) m/z 347 ($[\text{MH}^+]$, 80%); HRMS (CI) Calcd for $\text{C}_{22}\text{H}_{22}\text{N}_2\text{O}_2$ [M^+] 346.1681. Found: 346.1632.

Spiro[cyclopentane-1',3-[3H]indole]-2,3'(1H)-dione (41) and Spiro[cyclopentane-1',3-[3H]indole]-2,3'(1H)-dione-1-carboxamide (42)

A solution of racemic acid **32** (55.6 mg, 0.24 mmol), diphenylphosphoryl azide (DPPA) (0.11 mL, 4.8×10^{-4} mol) and NEt₃ (0.07 mL, 0.48 mmol) in anhydrous toluene (3 mL) was heated at 85°C for 3 h. The mixture was then heated at reflux for 30 min then 8.9 M HCl (0.05 mL) was cautiously added. The mixture was then heated at reflux for another 1 h before allowing to cool to RT with stirring for 15 h. The solvent was removed *in vacuo*. NMR analysis of the crude mixture revealed a 1:1 mixture of **41**:**42**, respectively. The crude mixture was purified by column chromatography in 30-50% EtOAc:PS and then a second time with 2:1:1 (DCM:PS:EtOAc). **41**: A semi-crystalline yellow oil (26.5 mg, 0.13 mmol, 54%), *R_f* 0.28 (50% EtOAc:PS). ¹H NMR (C₆D₆, 500 MHz) δ 8.81 (bs, 1H, NH), 6.96 (t, *J* 7.8 Hz, 1H, ArH-6), 6.79 (t, *J* 7.8 Hz, 1H, ArH-5), 6.66 (d, *J* 7.5 Hz, 1H, ArH-4), 6.55 (d, *J* 7.5 Hz, 1H, ArH-7), 2.53-2.62 (m, 1H, CH-4^α), 2.51 (d, *J* 17.5 Hz, 1H, CH-2^α), 2.06-2.15 (m, 1H, CH-4^β), 2.05 (d, *J* 18 Hz, 1H, CH-2^β), 2.01-2.06 (m, 1H, CH-5^α), 1.60 (dt, *J* 13, 8.5 Hz, 1H, CH-5^β). ¹³C NMR (C₆D₆, 125 MHz) δ 214.0 (C-3[′]), 182.7 (C-2), 141.0 (C-7a), 133.4 (C-3a), 128.4 (ArCH-6), 122.7 (ArCH-5), 122.5 (ArCH-4), 110.3 (ArCH-7), 51.1 (C-3), 46.7 (CH₂-2[′]), 36.5 (CH₂-4[′]), 33.4 (CH₂-5[′]). MS (EI) *m/z* 201 ([M⁺], 67%), 145 ([M⁺ - (CH₂)₂CO], 100%); HRMS (EI) Calcd for C₁₂H₁₂NO₂ [MH⁺] 202.0868. Found: 202.0874. **42**: White crystals (21.1 mg, 0.086 mmol, 35%), mp. 139-143°C, *R_f* 0.73 (50% EtOAc:PS). ¹H NMR (C₆D₆, 500 MHz) δ 8.64 (d, *J* 8 Hz, 1H, ArH-7), 7.96 (bs, 1H, NH_AH_B), 7.08 (t, *J* 8 Hz, 1H, ArH-6), 6.85 (t, *J* 7.5 Hz, 1H, ArH-5), 6.55 (d, *J* 7.5 Hz, 1H, ArH-4), 4.84 (bs, 1H, NH_AH_B), 2.37 (ddd, *J* 18, 9, 9 Hz, 1H, CH-4^α), 2.22 (d, *J* 18.5 Hz, 1H, CH-2^α), 2.01 (ddd, *J* 18.5, 9, 6 Hz, 1H, CH-4^β), 1.87 (d, *J* 18.5 Hz, 1H, CH-2^β), 1.68-1.74 (m, 1H, 1H, CH-5^α), 1.37-1.43 (m, 1H, 1H, CH-5^β). ¹³C NMR (C₆D₆, 125 MHz) δ 212.5 (C-3[′]), 182.0 (C-2), 152.1 (CONH₂), 139.9 (C-7a), 131.5 (C-3a), 128.8 (ArCH-6), 125.0 (ArCH-5), 121.6 (ArCH-4), 117.0 (ArCH-7), 51.3 (C-3), 47.0 (CH₂-2[′]), 36.1 (CH₂-4[′]), 34.0 (CH₂-5[′]). LRMS (EI) *m/z* 244 ([M⁺], 2%), 201 ([M⁺ - CONH₂], 36%); HRMS (EI) Calcd for C₁₃H₁₂N₂O₃ [M⁺] 244.0848. Found: 244.0823.

Ethyl (*S)-2-oxo-spiro[3'-cyclopentane-1',3-[3H]indole]-(3'*S**)-carboxylate (43) and Ethyl (*R**)-2-oxo-spiro[3'-cyclopentane-1',3-[3H]indole]-(3'*R**)-carboxylate (44)**

To a mixture of spiroalkene **15** (34.9 mg, 0.136 mmol) in EtOAc (2.2 mL) was added 10 wt. % palladium on activated carbon (9.4 mg). The system was then flushed with H₂ gas and left stirring under a H₂ atmosphere for 15 h. The crude reaction mixture was filtered on celite and washed multiple times with EtOAc. These organic extracts were evaporated *in vacuo*. NMR analysis of crude mixture revealed a 1.75:1 (**43**:**44**). The crude product was purified by column chromatography in 20-30% EtOAc:PS and then further by PTLC in 30% EtOAc:PS. **43**: A creamy white oil (20.1 mg, 0.78 μmol, 57%), *R_f* 0.28 (30% EtOAc:PS). ¹H NMR (500 MHz) δ 8.91 (bs, 1H, NH), 7.20 (t, *J* 7.7 Hz, 1H, ArH-6), 7.18 (d, *J* 7 Hz, 1H, ArH-4), 7.02 (t, *J* 7.7 Hz, 1H, ArH-5), 6.93 (d, *J* 7.5 Hz, 1H, ArH-7), 4.18 (q, *J* 7.3 Hz, 2H, CH₂CH₃), 3.25 (m, 1H, CH-3'_β), 2.51 (dd, *J* 13, 10 Hz, 1H, CH-2'_α), 2.28-2.40 (m, 3H, CH₂-4' and CH-5'_α), 2.14 (dd, *J* 13, 8 Hz, 1H, CH-2'_β), 1.84-1.95 (m, 1H, CH-5'_β), 1.28 (t, *J* 7.3 Hz, 3H, CH₃CH₂). ¹³C NMR (125 MHz) δ 183.1 (C-2), 174.4 (CO₂Et), 140.1 (C-7a), 136.1 (C-3a), 127.7 (ArCH-6), 122.53 (ArCH-4), 122.49 (ArCH-5), 109.8 (ArCH-7), 60.6 (CH₂CH₃), 54.3 (C-3), 44.8 (CH-3'_β), 40.8 (CH₂-2'), 37.3 (CH₂-5'), 29.6 (CH₂-4'), 14.2 (CH₃CH₂). MS (EI) *m/z* 259 ([M⁺], 72%), 260 ([MH⁺], 12%); HRMS (EI) Calcd for C₁₅H₁₇NO₃ [M⁺] 259.1208. Found: 259.1219. **44**: A yellow oil (6.9 mg, 0.26 μmol, 20%), *R_f* 0.38 (30% EtOAc:PS). ¹H NMR (C₆D₆, 500 MHz) δ 8.14 (bs, 1H, NH), 7.22 (d, 1H, *J* 7.5 Hz, ArH-4), 6.96 (dt, *J* 7.5, 1 Hz, 1H, ArH-6), 6.86 (dt, *J* 7.5, 1 Hz, 1H, ArH-5), 6.48 (d, *J* 8 Hz, 1H, ArH-7), 3.99 (q, *J* 7 Hz, 2H, CH₂CH₃), 3.38 (ddd, *J* 16, 16, 8 Hz, 1H, CH-3'_α), 2.43 (dd, *J* 13.5, 8.5 Hz, 1H, CH-2'_α), 2.33-2.38 (m, 1H, CH-4'_α), 2.31 (dd, *J* 14, 8 Hz, 1H, CH-2'_β), 2.19-2.25 (m, 1H, CH-4'_β), 2.10 (dt, *J* 13, 7.5 Hz, 1H, CH-5'_α), 1.87 (dt, *J* 12.5, 7.5 Hz, 1H, CH-5'_β), 0.96 (t, *J* 7 Hz, 3H, CH₃CH₂). ¹³C NMR (C₆D₆, 125 MHz) δ 183.6 (C-2), 175.2 (CO₂Et), 140.9 (C-7a), 135.6 (C-3a), 123.4 (ArCH-4), 127.7 (ArCH-6), 122.7 (ArCH-5), 109.5 (ArCH-7), 60.3 (CH₂CH₃), 54.3 (C-3), 44.5 (CH-3'_α), 40.6 (CH₂-2'), 38.1 (CH₂-5'), 30.8 (CH₂-4'), 14.2 (CH₃CH₂). LRMS (EI) *m/z* 259 ([M⁺], 64%), 260 ([MH⁺], 12%); HRMS (EI) Calcd for C₁₅H₁₇NO₃ [M⁺] 259.1208. Found: 259.1220.

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15. **CCDC depositions:** 266132 (**10**), 266133 (**16**), 266134 (**22**), 266135 (**25a**), 266136 (**27**), 266137 (**28**), 266138 (**42**), 268591 (**25b**), 268592 (**30**), 268593 (**31**), 268594 (**41**). See supporting Information for crystal/refinement data.
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Supporting information

Details of the X-ray Crystal/refinement data and experimental procedures for the synthesis of compounds **25b-37** (14 pages).

GRAPHICAL ABSTRACT**Synthesis of 2-Azaspiro[4.4]nonan-1-ones via Phosphine-catalysed [3+2]-Cycloadditions**

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Synthesis of 2-Azaspiro[4.4]nonan-1-ones *via* Phosphine-catalysed [3+2]-Cycloadditions

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SUPPORTING INFORMATION

Pages 1-3 X-ray data

Pages 4-14 Experimental procedures for the synthesis of compounds **25b-37**

X-ray Data

All single-crystal X-ray structure determinations were executed using full spheres of data from a Bruker AXS CCD area-detector instrument (ω -scans) fitted with a monochromatic MoK α radiation source ($\lambda = 0.71073$ Å) (Exception: **28**, which employed synchrotron radiation, $\lambda = 0.5500$ Å), $N_{\text{t(otal)}}$ reflections merging to N unique (R_{int} cited) after 'empirical'/multiscan absorption correction (proprietary software), N_o with $F > 4\sigma(F)$ considered 'observed' and used in the full matrix least squares refinement (reflection weights: $(\sigma^2(F) + 0.00 n_w F^2)^{-1}$). Molecular projections show non-hydrogen atoms with 50% probability amplitude displacement envelopes, hydrogen atoms having arbitrary radii of 0.1 Å. In all examples containing .CO.NH. components, the hydrogen is involved in a hydrogen-bond with that oxygen of a neighbouring molecule.

Crystal/refinement data: **10.** C₁₆H₂₃NO₅, $M = 309.4$. Triclinic, space group $P\bar{1}$ (#2), $a = 6.085(1)$, $b = 9.534(2)$, $c = 14.682(2)$ Å, $\alpha = 79.674(3)$, $\beta = 80.484(3)$, $\gamma = 77.536(3)^\circ$, $V = 811.0$ Å³. D_c ($Z = 2$) = 1.267 g cm⁻³. $\mu_{\text{Mo}} = 0.09$ mm⁻¹; specimen: 0.27 x 0.20 x 0.12 mm; $T'_{\text{min/max}} = 0.76$. $2\theta_{\text{max}} = 58^\circ$; $N_t = 7868$, $N = 3938$ ($R_{\text{int}} = 0.025$), $N_o = 2934$; $R = 0.047$, $R_w = 0.052$ ($n_w = 0.4$). $|\Delta\rho_{\text{max}}| = 0.34(3)$ e Å⁻³. (x, y, z, U_{iso})_H refined. T ca. 153 K. **(S)-16.** C₂₄H₂₈N₂O₇S, $M = 488.6$. Monoclinic, space group $P2_1$ (#4), $a = 12.085(5)$, $b = 7.243(1)$, $c = 13.924(2)$ Å, $\beta = 101.040(3)^\circ$, $V = 1196$ Å³. D_c ($Z = 2$) = 1.356 g cm⁻³. $\mu_{\text{Mo}} = 0.18$ mm⁻¹; specimen: 0.28 x 0.18 x 0.14 mm; $T'_{\text{min/max}} = 0.89$.

$2\theta_{\max} = 58^\circ$; $N_t = 11606$, $N = 3210$ ($R_{\text{int}} = 0.025$), $N_o = 2241$; $R = 0.053$, $R_w = 0.056$ ($n_w = 0.6$). $|\Delta\rho_{\max}| = 0.28(3) \text{ e } \text{\AA}^{-3}$. $x_{\text{abs}} = 0.06(16)$. *T ca.* 300 K. **22.** $\text{C}_{11}\text{H}_{15}\text{NO}_3$, $M = 209.3$. Triclinic, space group $P\bar{1}$, $a = 5.597(1)$, $b = 7.910(2)$, $c = 12.861(3) \text{ \AA}$, $\alpha = 86.683(5)$, $\beta = 79.353(5)$, $\gamma = 75.871(5)^\circ$, $V = 542.6 \text{ \AA}^3$. D_c ($Z = 2$) = 1.28_1 g cm^{-3} . $\mu_{\text{Mo}} = 0.09 \text{ mm}^{-1}$; specimen: $0.63 \times 0.12 \times 0.08 \text{ mm}$; $T'_{\min/\max} = 0.78$. $2\theta_{\max} = 58^\circ$; $N_t = 6707$, $N = 2861$ ($R_{\text{int}} = 0.027$), $N_o = 2274$; $R = 0.044$, $R_w = 0.051$ ($n_w = 0.3$). $|\Delta\rho_{\max}| = 0.36(3) \text{ e } \text{\AA}^{-3}$. *T ca.* 153 K. **25a.** $\text{C}_{22}\text{H}_{22}\text{N}_2\text{O}_2$, $M = 346.5$. Orthorhombic, space group $Pca2_1$ (#29), $a = 24.140(16)$, $b = 7.734(5)$, $c = 9.836(7) \text{ \AA}$, $V = 1836 \text{ \AA}^3$. D_c ($Z = 4$) = 1.25_3 g cm^{-3} . $\mu_{\text{Mo}} = 0.08 \text{ mm}^{-1}$; specimen: $0.13 \times 0.07 \times 0.03 \text{ mm}$; $T'_{\min/\max} = 0.76$. $2\theta_{\max} = 50^\circ$; $N_t = 13466$, $N = 1698$ ($R_{\text{int}} = 0.11$), $N_o = 1284$; $R = 0.066$, $R_w = 0.090$ ($n_w = 3$). $|\Delta\rho_{\max}| = 0.30(6) \text{ e } \text{\AA}^{-3}$. x_{abs} not refined. *T ca.* 153 K. **25b.** $\text{C}_{24}\text{H}_{27}\text{N}_3\text{O}_2$, $M = 389.5$. Triclinic, space group $P\bar{1}$, $a = 8.260(3)$, $b = 10.892(4)$, $c = 12.538(4) \text{ \AA}$, $\alpha = 67.764(6)$, $\beta = 82.723(6)$, $\gamma = 81.564(6)^\circ$, $V = 1030 \text{ \AA}^3$. D_c ($Z = 2$) = 1.25_6 g cm^{-3} . $\mu_{\text{Mo}} = 0.08 \text{ mm}^{-1}$; specimen: $0.12 \times 0.08 \times 0.04 \text{ mm}$; $T'_{\min/\max} = 0.88$. $2\theta_{\max} = 50^\circ$; $N_t = 9351$, $N = 3586$ ($R_{\text{int}} = 0.046$), $N_o = 2207$; $R = 0.057$, $R_w = 0.072$ ($n_w = 0.2$). $|\Delta\rho_{\max}| = 0.32(4) \text{ e } \text{\AA}^{-3}$. *T ca.* 153 K. **27.** $\text{C}_{15}\text{H}_{10}\text{N}_2\text{O}_2$, $M = 256.3$. Monoclinic, space group $P2_1/c$ (#14), $a = 8.204(2)$, $b = 18.128(5)$, $c = 8.914(2) \text{ \AA}$, $\beta = 107.823(4)^\circ$, $V = 1262 \text{ \AA}^3$. D_c ($Z = 4$) = 1.34_9 g cm^{-3} . $\mu_{\text{Mo}} = 0.09 \text{ mm}^{-1}$; specimen: $0.12 \times 0.08 \times 0.08 \text{ mm}$; $T'_{\min/\max} = 0.92$. $2\theta_{\max} = 50^\circ$; $N_t = 10582$, $N = 2207$ ($R_{\text{int}} = 0.065$), $N_o = 1747$; $R = 0.056$, $R_w = 0.081$ ($n_w = 2$). $|\Delta\rho_{\max}| = 0.30(5) \text{ e } \text{\AA}^{-3}$. *T ca.* 153 K. **28.** $\text{C}_{11}\text{H}_{15}\text{NO}_3$, $M = 209.3$. Monoclinic, space group $P2_1/c$, $a = 14.2396(11)$, $b = 6.2065(5)$, $c = 11.9144(9) \text{ \AA}$, $\beta = 102.276(4)^\circ$, $V = 1029 \text{ \AA}^3$. D_c ($Z = 4$) = 1.35_1 g cm^{-3} . $\mu_{\text{Mo}} = 0.06 \text{ mm}^{-1}$; specimen: not recorded; $T'_{\min/\max} = 1.00$. $2\theta_{\max} = 45^\circ$; $N_t = 28315$, $N = 2908$ ($R_{\text{int}} = 0.97$), $N_o = 2306$; $R = 0.043$, $R_w = 0.052$ ($n_w = 0.8$). $|\Delta\rho_{\max}| = 0.49(4) \text{ e } \text{\AA}^{-3}$. (x, y, z, U_{iso})_H refined. *T ca.* 120 K. **30.** $\text{C}_{16}\text{H}_{17}\text{NO}_3$, $M = 271.3$. Orthorhombic, space group $Pbca$ (# 61), $a = 11.667(7)$, $b = 10.836(6)$, $c = 21.167(12) \text{ \AA}$, $V = 2676 \text{ \AA}^3$. D_c ($Z = 8$) = 1.34_7 g cm^{-3} . $\mu_{\text{Mo}} = 0.09 \text{ mm}^{-1}$; specimen: $0.13 \times 0.06 \times 0.03 \text{ mm}$; $T'_{\min/\max} = 0.00$. $2\theta_{\max} = 50^\circ$; $N_t = 20960$, $N = 2394$ ($R_{\text{int}} = 0.16$), $N_o = 975$; $R = 0.087$, $R_w = 0.011$ ($n_w = 4.5$). $|\Delta\rho_{\max}| = 0.36(5) \text{ e } \text{\AA}^{-3}$. *Comment.* The carboxylate group was modelled as disordered over a pair of sites set at equal occupancy after trial refinement; the associated hydrogen bonding interactions appear to be with the C=O group oxygen of a neighbouring molecule. **31.** $\text{C}_{22}\text{H}_{22}\text{N}_2\text{O}_2$, $M = 346.4$. Triclinic, space group $P\bar{1}$, $a = 5.121(1)$, $b = 9.606(1)$, $c = 12.379(1) \text{ \AA}$, $\alpha = 69.657(3)$, $\beta = 81.925(3)$, $\gamma =$

$74.622(3)^\circ$, $V = 871.8 \text{ \AA}^3$. $D_c (Z = 2) = 1.32_0 \text{ g cm}^{-3}$. $\mu_{\text{Mo}} = 0.09 \text{ mm}^{-1}$; specimen: $0.25 \times 0.22 \times 0.04 \text{ mm}$; $T'_{\text{min/max}} = 0.89$. $2\theta_{\text{max}} = 65^\circ$; $N_t = 12099$, $N = 6128$ ($R_{\text{int}} = 0.025$), $N_o = 4580$; $R = 0.055$, $R_w = 0.077$ ($n_w = 3.5$). $|\Delta\rho_{\text{max}}| = 0.53(3) \text{ e \AA}^{-3}$. **41.** $\text{C}_{12}\text{H}_{11}\text{NO}_2$, $M = 201.2$. Triclinic, space group $P\bar{1}$, $a = 6.667(4)$, $b = 10.528(6)$, $c = 14.730(8) \text{ \AA}$, $\alpha = 105.632(9)$, $\beta = 98.876(10)$, $\gamma = 90.305(10)^\circ$, $V = 983 \text{ \AA}^3$. $D_c (Z = 4) = 1.36_0 \text{ g cm}^{-3}$. $\mu_{\text{Mo}} = 0.09 \text{ mm}^{-1}$; specimen: $0.13 \times 0.11 \times 0.03 \text{ mm}$; $T'_{\text{min/max}} = 0.74$. $2\theta_{\text{max}} = 50^\circ$; $N_t = 9300$, $N = 3355$ ($R_{\text{int}} = 0.25$), $N_o = 1645$; $R = 0.12$, $R_w = 0.25$ ($n_w = 2.5$). $|\Delta\rho_{\text{max}}| = 1.2(2) \text{ e \AA}^{-3}$. *Comment.* The conformations of the two C_5 rings differ slightly, the torsions being 'flat' in the bonds to either side of the CO group respectively. **42.** $\text{C}_{13}\text{H}_{12}\text{N}_2\text{O}_3$, $M = 244.3$. Monoclinic, space group $P2_1/n$ (#14), $a = 16.203(3)$, $b = 6.373(3)$, $c = 29.233(2) \text{ \AA}$, $\beta = 90.207(7)^\circ$, $V = 1156 \text{ \AA}^3$. $D_c (Z = 4) = 1.40_4 \text{ g cm}^{-3}$. $\mu_{\text{Mo}} = 0.10 \text{ mm}^{-1}$; specimen: $0.50 \times 0.10 \times 0.04 \text{ mm}$; $T'_{\text{min/max}} = 0.89$. $2\theta_{\text{max}} = 52^\circ$; $N_t = 7690$, $N = 2009$ ($R_{\text{int}} = 0.043$), $N_o = 1528$; $R = 0.059$, $R_w = 0.096$ ($n_w = 6$). $|\Delta\rho_{\text{max}}| = 0.62(4) \text{ e \AA}^{-3}$. $T \text{ ca. } 153 \text{ K}$.

Experimental procedures for the synthesis of compounds 25b-37

(5*S*^{*})-2-Benzyl-1-oxo-*N*-(*o*)-*N,N*-dimethylphenyl-2-azaspiro[4.4]non-7-ene-7-carboxamide (25b)

The title compound was prepared from **24** (48.5 mg, 0.18 mmol) and *N,N*-dimethylaminoaniline (26.8 mg, 0.2 mmol) using a similar method to that described for the above synthesis of **25a**, however the reaction mixture was allowed to stir under N₂ at RT for 15 h. The crude compound was purified by column chromatography in 70% EtOAc:PS to yield brown crystals (44.4 mg, 0.11 mmol, 64%), mp. 168-170°C, *R*_f 0.30 (70% EtOAc:PS). ¹H NMR (500 MHz) δ 7.39 (d, *J* 8.5 Hz, 2H, ArH-*o*'), 7.34 (t, *J* 7.3 Hz, 2H, ArH-*m*), 7.29 (t, *J* 7 Hz, 2H, ArH-*p*), 7.23 (d, *J* 7 Hz, 2H, ArH-*o*), 6.70 (d, *J* 9 Hz, 2H, ArH-*m*'), 6.47 (bs, 1H, CH=), 4.49 (ABq, *J* 15 Hz, 2H, NCH_ACH_BPh), 3.20 (q, *J* 6.3 Hz, 2H, CH₂-3), 3.14 (dd, *J* 15.5, 2.5 Hz, 1H, CH-6_β), 3.08 (dd, *J* 18, 2.5 Hz, 1H, CH-9_β), 2.92 (bs, 6H, N(CH₃)₂), 2.66 (d, *J* 15.5 Hz, 1H, CH-6_α), 2.47 (d, *J* 17.5 Hz, 1H, CH-9_α), 2.10-1.99 (m, 2H, CH₂-4). ¹³C NMR δ 178.1 (C-1), 148.3 (ArC-*p*'), 138.2 (C-7), 136.6 (ArC-*i*), 134.8 (CH=), 129.0 (ArCH-*m*), 128.3 (ArCH-*o*), 127.9 (ArCH-*p*), 127.7 (ArC-*i*'), 122.0 (ArCH-*o*'), 113.2 (ArCH-*m*'), 50.7 (C-5), 47.3 (NCH₂Ph), 43.9 (CH₂-3), 43.8 (CH₂-9), 42.6 (CH₂-6), 41.1 (N(CH₃)₂), 35.5 (CH₂-4). MS (CI) *m/z* 390 ([MH⁺], 100%); HRMS (CI) Calcd for C₂₄H₂₈N₃O₂ [MH⁺] 390.2181. Found: 390.2170.

(5*S*^{*})-1-Oxo-2-azaspiro[4.4]non-7-ene-7-carboxylic acid (26)

The title compound was prepared from **22** (90.5 mg, 0.43 mmol) using a similar method to that described above for the synthesis of **24**. Compound **26** was obtained as brown crystals (41.6 mg, 0.23 mmol, 53%), mp. 168°C, *R*_f 0.03 (EtOAc). ¹H NMR δ 6.79 (bs, 1H, NH), 6.68 (s, 1H, CH=), 3.68-3.76 (m, 2H, NCH₂), 3.03 (overlapping d, *J* 14.4 Hz, 2H, CH-6_β, CH-9_β), 2.59 (d, *J* 15 Hz, 1H, CH-6_α), 2.47 (d, *J* 18 Hz, 1H, CH-9_α), 2.04-2.21 (m, 2H, CH₂-4). ¹³C NMR δ 181.7 (C-1), 165.0 (CO₂H), 141.2 (CH=), 134.1 (C-7), 49.4 (C-5), 43.7 (CH₂-9), 42.1 (CH₂-6), 39.5 (NCH₂), 37.9

(CH₂-4). MS (CI) m/z 182 ([MH⁺], 100%); HRMS (CI) Calcd for C₉H₁₂NO₃ [MH⁺] 182.0817. Found: 182.0818.

(5S^{*})-1-Oxo-N-phenyl -2-azaspiro[4.4]non-7-ene-7-carboxamide (27)

The title compound was prepared by two methods. **Method 1:** The title compound was prepared from **26** (38 mg, 0.21 mmol) and aniline (0.02 mL, 0.22 mmol) using a similar method to that described above for the synthesis of **25a**. Compound **27** was obtained as a yellow solid, mp. 148-150 °C after purification by column chromatography in 5% MeOH:EtOAc (48.9 mg, 1.91×10^{-4} mol, 91%), R_f 0.23 (5% MeOH:EtOAc). **Method 2:** To a solution of spiroamide **35** (75.7 mg, 0.16 mmol) was added anisole (0.18 mL, 1.65 mmol) and TFA (1.5 mL). The reaction was left to stir for 15 h. The volatiles were then removed and residue dissolved in CHCl₃ (10 mL) and poured slowly onto sat. Na₂CO₃ solution. The mixture was repeatedly extracted with CHCl₃ to yield a yellow oil (23.1 mg, 0.09 mmol, 57%). ¹H NMR δ 7.55 (d, J 9 Hz, 2H, ArH), 7.26-7.35 (m, 2H, ArH), 7.10 (t, J 7.3 Hz, 1H, ArH), 6.50 (s, 1H, CH=), 6.15 (bs, 1H, CONHPh), 3.37 (t, J 6.6 Hz, 2H, NCH₂), 3.14 (dd, J 15.7, 2.5 Hz, 1H, CH-6 β), 3.05 (dd, J 18.1, 2.5 Hz, 1H, CH-9 β), 2.71 (d, J 16.2 Hz, 1H, CH-6 α), 2.52 (d, J 18.3 Hz, 1H, CH-9 α), 2.08-2.26 (m, 2H, CH₂-4). ¹³C NMR δ 183.0 (C-1), 166.0 (CO₂NHPh), 137.7 (C-7), 134.9 (CH=), 130.3 (ArC-*i*), 128.8 (ArCH-*m*), 124.2 (ArCH-*p*), 119.8 (ArCH-*o*), 49.1 (C-5), 43.3 (CH₂-9), 42.1 (CH₂-6), 39.2 (NCH₂), 37.4 (CH₂-4). MS (CI) m/z 257 ([MH⁺], 32%); HRMS (CI) Calcd for C₁₅H₁₆N₂O₂ [M⁺] 256.1212. Found: 256.1227.

Ethyl (5R^{*})-1-oxo-2-azaspiro[4.4]non-6-ene-6-carboxylate (28)

The title compound was prepared from **10** (337.8 mg, 1.09 mmol) in dry DCM (1 mL) and the addition of TFA (1 mL) as described for the above synthesis of **22**. The organic portions were dried, and evaporated *in vacuo* to yield compound **28** as white needle-like crystals (197.0 mg, 0.94 mmol, 86%), mp. 102-104°C, R_f 0.13 (70% EtOAc:PS). ¹H NMR δ 6.99 (t, J 2.7 Hz, 1H, CH=), 4.18 (q, J 7.2 Hz, 2H, CH₂CH₃), 3.50 (ddt, J 9.3, 3.6, 0.9 Hz, 1H, NCH_ACH_B), 3.35 (dt, J 9.3, 7.8 Hz, 1H,

$\text{NCH}_\text{A}\text{CH}_\text{B}$), 2.68 (ddd, J 9.3, 4.5, 2.7 Hz, 1H, $\text{CH}_\text{A}\text{CH}_\text{B-8}$), 2.62 (ddd, J 9.3, 4.2, 2.7 Hz, 1H, $\text{CH}_\text{B}\text{CH}_\text{A-8}$), 2.59-2.46 (m, 1H, $\text{CH}_\text{A}\text{CH}_\text{B-4}$), 2.44-2.37 (m, 1H, $\text{CH}_\text{A}\text{CH}_\text{B-9}$), 2.09-2.01 (m, 1H, $\text{CH}_\text{B}\text{CH}_\text{A-4}$), 1.99 (ddd, 12.6, 8.1, 4.5 Hz, 1H, $\text{CH}_\text{B}\text{CH}_\text{A-9}$), 1.28 (ddt, 3H, J 7.2, 7.2, 3 Hz, 3H, CH_2CH_3). ^{13}C NMR (125 MHz) δ 180.9 (C-1), 163.7 (CO_2Et), 147.0 (CH=), 137.8 (C-6), 60.1 (CH_2CH_3), 55.8 (C-5), 39.7 (NCH_2), 36.4 (CH_2-9), 32.9 (CH_2-4), 31.2 (CH_2-8), 14.0 (CH_2CH_3). MS (CI) m/z 210 ($[\text{MH}^+]$, 53%); HRMS (CI) Calcd for $\text{C}_{11}\text{H}_{16}\text{NO}_3$ $[\text{MH}^+]$ 210.1130. Found: 210.1133.

Ethyl (5*R*^{*})-2-benzyl-1-oxo-2-azaspiro[4.4]non-6-ene-6-carboxylate (29)

The title compound was prepared from **28** (129 mg, 0.62 mmol) as described for the synthesis of **23** however the reaction mixture was left stirring for 5 h. The crude product was purified by column chromatography using 50% EtOAc:PS as the eluent to give a **29** as a yellow oil (87.3 mg, 0.3 mmol, 47%), R_f 0.42 (50% EtOAc:PS). ^1H NMR δ 7.23-7.36 (m, 5H, ArH), 6.99 (t, J 2.5 Hz, 1H, CH=), 4.50 (ABq, J 17.4 Hz, 2H, $\text{NCH}_\text{A}\text{CH}_\text{B}\text{Ph}$), 4.08-4.23 (m, 2H, CH_2CH_3), 3.35 (dt, J 9.4, 3.9 Hz, 1H, $\text{CH}_\text{A}\text{CH}_\text{B-3}$), 3.21 (ddd, J 9.3, 8.4, 6.9 Hz, 1H, $\text{CH}_\text{B}\text{CH}_\text{A-3}$), 2.61-2.73 (m, 1H, $\text{CH}_\text{A}\text{CH}_\text{B-8}$), 2.55 (ddd, J 8.7, 6.3, 2.4 Hz, 1H, $\text{CH}_\text{B}\text{CH}_\text{A-8}$), 2.33-2.46 (om, 2H, $\text{CH}_\text{A}\text{CH}_\text{B-9}$ and $\text{CH}_\text{A}\text{CH}_\text{B-4}$), 1.89-2.00 (m, 2H, $\text{CH}_\text{B}\text{CH}_\text{A-9}$ and $\text{CH}_\text{B}\text{CH}_\text{A-4}$), 1.22-1.29 (m, 3H, CH_2CH_3). ^{13}C NMR δ 176.9 (C-1), 163.8 (CO_2Et), 147.0 (CH=), 138.3 (C-7), 136.6 (ArC-*i*), 128.5 (ArCH-*m*), 128.0 (ArCH-*o*), 127.3 (ArCH-*p*), 60.2 (CH_2CH_3), 56.7 (C-5), 47.0 (NCH_2Ph), 44.2 (CH_2-3), 36.9 (CH_2-9), 31.2 (CH_2-8), 30.5 (CH_2-4), 14.1 (CH_2CH_3). MS (CI) m/z 300 ($[\text{MH}^+]$, 8%); HRMS (EI) Calcd for $\text{C}_{18}\text{H}_{21}\text{NO}_3$ $[\text{M}^+]$ 299.1521. Found: 299.1508.

(5*R*^{*})-2-Benzyl-1-oxo-2-azaspiro[4.4]non-6-ene-6-carboxylic acid (30)

The title compound was prepared from **29** (87.3 mg, 0.3 mmol) as described for the synthesis of **24** to yield white needle-like crystals (63.3 mg, 0.23 mmol, 80%) which were purified by recrystallisation from 1% MeOH:EtOAc to yield white needle-like crystals (22.2 mg, 82 μmol , 28%), mp. 200°C. ^1H NMR (CD_3OD , 500 MHz) δ 7.25-7.34 (m, 5H, ArH), 6.99 (t, J 2.5 Hz, 1H,

$\underline{\text{CH}}=$), 4.48 (ABq, J 14.7 Hz, 2H, $\text{NCH}_\text{A}\underline{\text{CH}}_\text{B}\text{Ph}$), 3.25-3.39 (m, 2H, $\underline{\text{CH}}_2$ -3), 2.59 (dt, J 7.25, 2.5 Hz, 1H, $\underline{\text{CH}}_2$ -8), 2.37 (ddd, J 13, 9, 8 Hz, 1H, $\underline{\text{CH}}_\text{A}\text{CH}_\text{B}$ -4), 2.28 (ddd, J 12.5, 8.75, 8.5 Hz, 1H, $\underline{\text{CH}}_\text{A}\text{CH}_\text{B}$ -9), 2.00-2.08 (m, 2H, $\underline{\text{CH}}_\text{B}\text{CH}_\text{A}$ -9 and $\underline{\text{CH}}_\text{B}\text{CH}_\text{A}$ -4). ^{13}C NMR (CD_3OD , 125 MHz) δ 180.0 (C-1), 167.7 ($\underline{\text{CO}}_2\text{H}$), 148.6 ($\underline{\text{CH}}=$), 137.6 (C-7), 139.9 ($\text{ArC}-i$), 129.7 ($\text{ArCH}-m$), 128.9 ($\text{ArCH}-o$), 128.6 ($\text{ArCH}-p$), 58.8 (C-5), 47.8 (NCH_2Ph), 45.6 ($\underline{\text{CH}}_2$ -3), 37.3 ($\underline{\text{CH}}_2$ -9), 32.1 ($\underline{\text{CH}}_2$ -8), 31.4 ($\underline{\text{CH}}_2$ -4). MS (CI) m/z 272 ($[\text{MH}^+]$, 100%); HRMS (CI) Calcd for $\text{C}_{16}\text{H}_{17}\text{NO}_3$ $[\text{M}^+]$ 271.1208. Found: 271.1123.

(5*R*^{*})-2-Benzyl-1-oxo-*N*-phenyl-2-azaspiro[4.4]non-6-ene-6-carboxamide (31)

The title compound was prepared from **30** (22.2 mg, 82 μmol) as described for the synthesis of **25a** however the reaction mixture was left stirring at 60°C for 2d and then another equivalent of EDCI (16.2 mg, 82 μmol) was added and the reaction was left to stir for 60°C for 4d under N_2 . The crude product was purified by column chromatography using 60-100% EtOAc:PS to yield white crystals (27.4 mg, 79 μmol , 97%), mp. 164-165°C, R_f 0.18 (60% EtOAc:PS). ^1H NMR δ 8.38 (bs, 1H, NH), 7.52 (d, J 7.5 Hz, 2H, $\text{ArH}-o'$), 7.24-7.29 (m, 7H, ArH), 7.06 (t, J 7.35 Hz, 1H, $\text{ArH}-p$), 6.68 (bs, 1H, $\underline{\text{CH}}=$), 4.53 (ABq, J 14.7 Hz, 2H, $\text{NCH}_\text{A}\underline{\text{CH}}_\text{B}\text{Ph}$), 3.39 (dt, J 9.3, 3 Hz, 1H, $\underline{\text{CH}}_\text{A}\text{CH}_\text{B}$ -3), 3.24 (dd, J 17.4, 7.8 Hz, 1H, $\underline{\text{CH}}_\text{B}\text{CH}_\text{A}$ -3), 2.54-2.62 (m, 2H, $\underline{\text{CH}}_2$ -8), 2.49 (dt, J 12, 8.4 Hz, 1H, $\underline{\text{CH}}_\text{A}\text{CH}_\text{B}$ -4), 2.34 (ddd, 12.6, 9, 8.1 Hz, 1H, $\underline{\text{CH}}_\text{A}\text{CH}_\text{B}$ -9), 1.93-2.01 (om, 2H, $\underline{\text{CH}}_\text{B}\text{CH}_\text{A}$ -9 and $\underline{\text{CH}}_\text{B}\text{CH}_\text{A}$ -4). ^{13}C NMR δ 177.9 (C-1), 163.6 ($\underline{\text{CONHPh}}$), 142.4 (C-7), 139.9 ($\underline{\text{CH}}=$), 138.3 ($\text{ArC}-i'$), 136.5 ($\text{ArC}-i$), 129.0 (ArCH), 128.9 (ArCH), 128.1 (ArCH), 127.7 ($\text{ArCH}-p$), 124.2 ($\text{ArCH}-p'$), 120.2 ($\text{ArCH}-o'$), 58.8 (C-5), 47.4 (NCH_2Ph), 44.7 ($\underline{\text{CH}}_2$ -3), 36.4 ($\underline{\text{CH}}_2$ -9), 31.3 ($\underline{\text{CH}}_2$ -8), 30.7 ($\underline{\text{CH}}_2$ -4). MS (CI) m/z 347 ($[\text{MH}^+]$, 57%), 346 ($[\text{M}^+]$, 26%), 225 ($[\text{M}^+ - \text{CONHPh}]$, 17%), 149 ($[\text{M}^+ - (\text{CONHPh}, \text{Ph})]$, 45%); HRMS (CI) Calcd for $\text{C}_{22}\text{H}_{22}\text{N}_2\text{O}_2$ $[\text{M}^+]$ 346.1681. Found: 346.1671.

2-Oxo-spiro[3'-cyclopentene-1',3-[3H]indole]-3'-carboxylic acid (32)

The title compound was prepared from **15** (34.7 mg, 0.14 mmol) using a similar method to that described for the synthesis of **24**. However the mixture was left stirring at 60°C for 5 h and no further additions of K₂CO₃ were needed. After extraction, the compound required no further purification yielding a creamy brown solid (29.9 mg, 0.13 mmol, 94%), mp. 108-110°C, R_f 0.38 (EtOAc). ¹H NMR δ 9.13 (bs, 1H, NH), 7.23 (d, *J* 7.8 Hz, 1H, ArH-4), 7.22 (t, *J* 7.6 Hz, 1H, ArH-6), 7.03 (t, *J* 7.6 Hz, 1H, ArH-5), 6.98 (s, 1H, CH=), 6.94 (d, *J* 7.5 Hz, 1H, ArH-7), 3.28 (dd, *J* 16.5, 2.7 Hz, 1H, CH-2_α), 3.22 (dd, *J* 16.5 Hz, 2.1 Hz, 1H, CH-5_α), 2.91 (d, *J* 16.5 Hz, 1H, CH-2_β), 2.83 (d, *J* 18.9 Hz, 1H, CH-5_β). ¹³C NMR δ 183.6 (C-2), 168.5 (CO₂H), 143.1 (CH=), 139.5 (C-7a), 136.4 (C-3a), 134.4 (C-3'), 128.2 (ArCH-6), 123.3 (ArCH-5), 122.1 (ArCH-4), 110.1 (ArCH-7), 52.7 (C-3), 45.0 (CH₂-5'), 43.0 (CH₂-2'). MS (EI) *m/z* 229 ([M⁺], 12%), 211 ([M⁺ - H₂O], 6%), 183 ([M⁺ - COOH], 14%); HRMS (EI) Calcd for C₁₃H₁₁NO₃ [M⁺] 229.0739. Found: 229.0744.

2-Oxo-*N*-phenyl-spiro[3'-cyclopentene-1',3-[3H]indole]-3'-carboxamide (**33a**)

The title compound was prepared using two methods. **Method 1:** The title compound was prepared from **32** (29.3 mg, 0.13 mmol) and aniline (0.02 mL, 0.22 mmol) using a similar method to that described for the above synthesis of **25a**, however the reaction mixture was allowed to stir under N₂ at RT for 15 h. The crude compound was extracted with DCM, and washed with water and brine. The organic extracts were dried with MgSO₄ and solvent evaporated *in vacuo* to yield white crystals (35.8 mg, 0.12 mmol, 92%), mp. 184°C, R_f 0.13 (40% EtOAc:PS). **Method 2:** To a solution of the amide **37** (12.4 mg, 0.029 mmol) in dry DCM was added sequentially anisole (0.03 mL, 0.3 mmol) and TFA (0.28 mL, 3.6 mmol). The reaction was left stirring for 15 h. The volatiles were then removed, residue dissolved in CHCl₃ and poured slowly onto a saturated Na₂CO₃ solution. The crude mixture was repeatedly extracted with CHCl₃. The solvent was evaporated *in vacuo* to yield white crystals (4.6 mg, 1.5 × 10⁻⁵ mol, 52%), mp. 184°C. ¹H NMR δ 8.87 (bs, 1H, NH), 7.78 (bs, 1H, CONHPh), 7.58 (d, *J* 8.1 Hz, 2H, ArH-*o*), 7.32 (t, *J* 7.8 Hz, 2H, ArH-*m*), 7.24 (d, *J* 7.8 Hz, 1H, ArH-4), 7.20 (t, *J* 7.2 Hz, 1H, ArH-6), 7.10 (t, *J* 7.5 Hz, 1H, ArH-*p*), 7.01 (t, *J* 7.6 Hz, 1H, ArH-5),

6.91 (d, J 7.8 Hz, 1H, ArH-7), 6.68 (s, 1H, CH=), 3.32 (dd, J 16, 2.1 Hz, 1H, CH-2 α), 3.18 (d, J 18.3, 2.1 Hz, 1H, CH-5 α), 3.00 (d, J 16.2 Hz, 1H, CH-2 β), 2.82 (d, J 18 Hz, 1H, CH-5 β). ^{13}C NMR δ 182.9 (C-2), 162.5 (CONH), 139.7 (C-7a), 138.2 (C-3'), 137.6 (ArC-*i*), 136.1 (C-3a), 135.6 (CH=), 129.0 (ArCH-*m*), 128.2 (ArCH-6), 124.4 (ArCH-*p*), 123.2 (ArCH-5), 122.3 (ArCH-4), 120.1 (ArCH-*o*), 109.9 (ArCH-7), 52.5 (C-3), 44.8 (CH₂-5'), 43.5 (CH₂-2'). MS (EI) m/z 304 ([M⁺], 8%), 184 ([M⁺-CONHPh], 92%), 159 [M⁺-CONHPhC=CH], 97%); HRMS (EI) Calcd for C₁₉H₁₆N₂O₂ [M⁺] 304.1212. Found: 304.1207.

2-Oxo-*N*-(*o*)-*N,N*-dimethylphenyl-spiro[3'-cyclopentene-1',3-[3H]indole]-3'-carboxamide (33b)

The title compound was prepared from **32** (23.8 mg, 0.1 mmol) and *N,N*-dimethylaminoaniline (24.1 mg, 0.2 mmol) using a similar method to that described for the above synthesis of **33a**, however the reaction mixture was allowed to stir under N₂ at RT 15 h. The crude compound was purified by column chromatography using 50-70% EtOAc:PS to yield a black powder (15.9 mg, 45 μmol , 44%), R_f 0.73 (80% EtOAc:PS). ^1H NMR δ 8.35 (bs, 1H, NH-1), 7.40 (d, J 9.3 Hz, 2H, ArH-*o*), 7.40 (bs, 1H, NHPhNMe₂), 7.26 (d, J 7.2 Hz, 1H, ArH-4), 7.20 (dt, J 7.5, 1.5 Hz, 1H, ArH-6), 7.02 (dt, J 7.5, 0.9 Hz, 1H, ArH-5), 6.90 (d, J 7.5 Hz, 1H, ArH-7), 6.69 (d, J 9 Hz, 2H, ArH-*m*), 6.64 (bs, 1H, CH=), 3.33 (dd, J 16, 2.2 Hz, 1H, CH-2 α), 3.19 (dq, J 18, 2.4 Hz, 1H, CH-5 α), 2.98 (d, J 15.9 Hz, 1H, CH-2 β), 2.91 (bs, 6H, N(CH₃)₂), 2.82 (d, J 17.4 Hz, 1H, CH-5 β). ^{13}C NMR δ 182.6 (C-2), 162.1 (=CCO), 148.1 (ArC-*p*), 139.6 (C-7a), 138.3 (C-3'), 136.4 (C-3a), 135.0 (CH=), 128.2 (ArCH-6), 127.3 (ArC-*i*), 123.1 (ArCH-5), 122.4 (ArCH-4), 121.9 (ArCH-*o*), 112.9 (ArCH-*m*), 109.8 (ArCH-7), 52.6 (C-3), 44.9 (CH₂-5'), 43.6 (CH₂-2'), 40.8 (N(CH₃)₂). MS (EI) m/z 347 ([M⁺], 3%), 167 (35%), 149 (100%); HRMS (EI) Calcd for C₂₁H₂₁N₃O₂ [M⁺] 347.1634. Found 347.1633.

***N*-(4-Methoxybenzyl)-*N*-phenyl but-2-ynamide (7c)**

The title compound was prepared from *N*-(4-methoxybenzyl)-*N*-phenylamine (117 mg, 0.6 mmol) and 2-butynoic acid (50.7 mg, 0.6 mmol) using a similar method to that described for the synthesis of **25a**. However the reaction mixture was left stirring RT for 15 h. The crude product was purified by gradient column chromatography using 10-50% EtOAc:PS as the eluent to yield **7c** as a brown oil (296.5 mg, 1.06 mmol, 66%), R_f 0.62 (50% EtOAc:PS). ^1H NMR δ 7.29-7.31 (m, 2H, ArH-*m*), 7.11 (d, J 8.7 Hz, 2H, ArH-*o*), 7.04-7.07 (m, 1H, ArH-*p*), 7.06 (d, J 7.8 Hz, 2H, ArH-*o*), 6.78 (d, J 8.7 Hz, 2H, ArH-*m*), 4.86 (s, 2H, NCH₂), 3.77 (s, 3H, OCH₃), 1.70 (s, 3H, CCH₃). ^{13}C NMR δ 158.9 (ArC-*p*), 154.3 (CONH), 141.6 (ArC-*i*), 130.1 (ArCH-*o*), 129.0 (ArC-*i*), 128.8 (ArCH-*m*), 128.4 (ArCH-*o*), 127.8 (ArCH-*p*), 113.7 (ArCH-*m*), 90.3 (C $\equiv$ CCH₃), 74.1 (C $\equiv$ CCH₃), 55.0 (OCH₃), 51.5 (NCH₂), 3.68 (CCH₃). MS (ES) m/z 280.2 ([MH⁺], 99%); HRMS (EI) Calcd for C₁₈H₁₇NO₂ [M⁺] 279.1259. Found: 279.1280.

(5S^{*})-2-tert-Butoxycarbonyl-*N*-phenyl-*N*-(4-methoxybenzyl)-1-oxo-2-azaspiro[4.4]non-7-ene-7-carboxamide (35)

The title compound was prepared using a similar method described above for the synthesis of **9** and **10** from **4** (190 mg, 0.97 mmol) and **7c** (296.5 mg, 1.06 mmol) instead of ethyl 2-butynoate. The crude compound was then purified by gradient column chromatography using 10-90% EtOAc:PS as eluent to yield **35** as a brown oil (64.3 mg, 0.13 mmol, 14%), R_f 0.59 (50% EtOAc:PS). ^1H NMR (500 MHz) δ 7.22-7.33 (m, 3H, ArH-*m* and ArH-*p*), 7.13 (d, J 7 Hz, 2H, ArH-*o*), 6.97 (dd, J 8.5, 2H, ArH-*o*), 6.78 (d, J 9 Hz, 2H, ArH-*m*), 5.56 (s, 1H, CH=), 4.89 (s, 2H, NCH₂), 3.77 (s, 3H, OCH₃), 3.50-3.58 (m, 2H, CH₂-3), 2.74 (d, J 18 Hz, 1H, CH-9 β), 2.73 (d, J 14.7 Hz, 1H, CH-6 β), 2.26 (d, J 14.4 Hz, 1H, CH-6 α), 2.18 (d, J 18.3 Hz, 1H, CH-9 α), 1.71-1.73 (m, 2H, CH₂-4), 1.52 (s, 9H, C(CH₃)₃). ^{13}C NMR δ 177.0 (C-1), 166.2 (CONPhPMB), 158.7 (ArC-*p*), 150.2 (NCO₂), 142.5 (ArC-*i*), 136.5 (C-7), 135.1 (CH=), 129.9 (ArCH-*o*), 129.3 (ArC-*i*), 129.1 (ArCH-*m*), 127.9 (ArCH-*o*), 127.5 (ArCH-*p*), 113.6 (ArCH-*m*), 82.8 (C(CH₃)₃), 55.1 (OCH₃), 52.9 (NCH₂), 51.5 (C-5), 43.8 (CH₂-9), 43.1 (CH₂-6), 43.0 (CH₂-3), 33.2 (CH₂-4), 27.9 C(CH₃)₃. MS (ES) m/z 499 ([MH⁺]

+ Na⁺], 12%), 477.3 ([MH⁺], 12%), 377.3 ([MH⁺ -(Boc, CH₃)], 100%); HRMS (ES) Calcd for C₂₈H₃₃N₂O₅ [MH⁺] 477.2389. Found: 477.2412.

Methyl 3-[(4-Methoxyphenyl)phenylcarbamoyl]-1-(2-nitrophenyl)-cyclopent-3-enecarboxylate (36)

To a solution of alkene **6** (26 mg, 0.12 mmol) and amide **7c** (39.1 mg, 0.14 mmol) in dry benzene (3 mL) was slowly added tributylphosphine (0.02 mL, 80 μmol). The reaction was left to stir for 2d. Upon evaporation *in vacuo* of volatiles the resulting crude product was purified by column chromatography using 30-50% EtOAc:PS as eluent to yield a yellow oil (33.4 mg, 0.069 mmol, 55%), R_f 0.65 (40% EtOAc:PS). ¹H NMR (C₆D₆, 500 MHz) δ 7.52 (d, *J* 8 Hz, 1H, ArH-3), 7.25 (d, *J* 8.5 Hz, 2H, ArH-*o*'), 7.10 (d, *J* 8.5 Hz, 1H, ArH-6), 6.90 (t, *J* 7.5 Hz, 1H, ArH-5), 6.86-6.88 (m, 3H, ArH-*m* and ArH-*p*), 6.72-6.74 (m, 4H, ArH-*m*' and ArH-*o*), 6.67 (t, *J* 7.7 Hz, 1H, ArH-4), 5.44 (s, 1H, CH=), 4.94 (ABq, *J* 14.5 Hz, 2H, NCH₂), 3.54 (dd, *J* 17, 2 Hz, 1H, CH-2'α), 3.32 (dd, *J* 18.5 Hz, 1H, CH-5'α), 3.28 (s, 6H, CO₂CH₃ and OCH₃), 3.18 (d, *J* 17.5 Hz, 1H, CH-2'β), 2.45 (d, *J* 18.5 Hz, 1H, CH-5'β). ¹³C NMR (C₆D₆, 125 MHz) δ 173.8 (CO₂Me), 165.7 (CON), 159.5 (ArC-*p*'), 148.8 (ArC-2), 143.2 (ArC-*i*'), 138.7 (ArC-1), 137.1 (C-3'), 134.7 (CH=), 132.7 (ArCH-5), 130.6 (ArCH-*o*'), 130.1 (ArC-*i*'), 129.2 (ArCH-*m*), 128.7 (ArCH-6), 128.3 (ArCH-*o*), 127.5 (ArCH-4), 127.2 (ArCH-*p*), 125.1 (ArCH-3), 114.1 (ArCH-*m*'), 55.4 (C-1'), 54.6 (CO₂CH₃), 53.1 (NCH₂), 51.9 (OCH₃), 47.0 (CH₂-2'), 45.9 (CH₂-5'). MS (ES) *m/z* 487 (15%) [MH⁺], 455 (18%) [M⁺ - OMe]; HRMS (ES) Calcd for C₂₈H₂₇N₂O₆ [MH⁺] 487.1869. Found 487.1871.

2-Oxo-*N*-phenyl-*N*-(4-methoxybenzyl)-spiro[3'-cyclopentene-1',3-[3H]indole]-3'-carboxamide (37)

To a stirred solution of **36** (87.8 mg, 0.18 mmol) in acetic acid (15 mL) was added activated Zn dust (40 mg, 0.61 mmol). After 1.5 h, the solution was filtered through celite and the filtrate was then washed with sat. Na₂CO₃ solution and then extracted with EtOAc to yield **37** as a brown oil (12.4

mg, 0.029 mmol, 16%, $R_f = 0.63$ in 70% EtOAc:PS). ^1H NMR (C_6D_6 , 500 MHz) δ 7.99 (bs, 1H, NH), 7.26 (d, J 8.5 Hz, 2H, ArH- o'), 6.96 (t, J 7.5 Hz, 2H, ArH- m), 6.94 (t, J 6.5 Hz, 1H, ArH-6), 6.88-6.90 (m, 1H, ArH- p), 6.88 (d, J 7 Hz, 1H, ArH-4), 6.81 (d, J 7.5 Hz, 2H, ArH- o), 6.77 (t, J 7.8 Hz, 1H, ArH-5), 6.74 (d, J 8.5 Hz, 2H, ArH- m'), 6.43 (d, J 8 Hz, 1H, ArH-7), 5.69 (s, 1H, CH=), 4.95 (ABq, J 14 Hz, 2H, NCH₂), 3.29 (s, 3H, OCH₃), 3.23 (dd, J 16, 2.5 Hz, 1H, CH-2' _{α}), 2.88 (dd, J 18, 2.5 Hz, 1H, CH-5' _{α}), 2.71 (d, J 16.5 Hz, 1H, CH-2' _{β}), 2.18 (d, J 17.5 Hz, 1H, CH-5' _{β}). ^{13}C NMR (C_6D_6 , 125 MHz) δ 182.0 (C-2), 165.9 (CON), 159.5 (ArC- p'), 143.4 (ArC- i), 140.4 (C-7a), 138.3 (C-3'), 137.1 (C-3a), 135.3 (CH=), 130.6 (ArCH- o'), 130.3 (ArC- i'), 129.3 (ArCH- m), 128.5 (ArCH- o), 128.3 (ArCH-6), 127.2 (ArCH- p), 122.6 (ArCH-5), 122.3 (ArCH-4), 114.1 (ArCH- m'), 109.6 (ArCH-7), 54.6 (CH₃), 53.1 (NCH₂), 52.5 (C-3), 46.0 (CH₂-2'), 44.8 (CH₂-5). MS (CI) m/z 425 ([MH⁺], 37%); HRMS (EI) Calcd for C₂₇H₂₄N₂O₃ [M⁺] 424.1787. Found: 424.1786.