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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-butynoic 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

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Abstract: The phosphine-catalysed [3+2]-cycloaddition of the 2-methylene $\gamma$-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-butynoic acid (7\textsubscript{a-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 spirocyclic ketones, 41 and 42.

Key words: phosphine-catalysed, [3+2]-cycloaddition, 2-methylene $\gamma$-lactams, spiroheterocyclics, 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'(2'H)-one (2) or spiro[3H-indole-3,3'-pyrrolidin]-2(1H)-one (3) ring system.\textsuperscript{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-butyric acid with either 2-methylene \( \gamma \)-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 the chiral (1S)-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-butyrate with electron-deficient alkenes has been established as a useful method for preparing substituted cyclopentenes\(^3\)\(^{-13}\) 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.\(^{13}\)
2. Results and Discussion

The results of the phosphine-catalysed [3+2]-cycloaddition reactions of the 2-methylene \( \gamma \)-lactams 4 and 5 with the ylide 8a (\( X = \text{OEt} \)), that was generated \textit{in situ} from the reaction of ethyl 2-butyroate 7a and tributylphosphine (TBP) are shown in Scheme 2. The reaction of 4\( ^{13} \) with ethyl 2-butyroate (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 \textit{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).\textsuperscript{12,13}
Scheme 2 (compounds 9 and 10 are racemic)

4; R = H  
5; R = CO₂Et

regioisomer A  
regioisomer B

9; R = H (51%)  
11; R = CO₂Et (28%)  
[10; R = H (21%)  
[X-ray]  
12; R = CO₂Et  
13 (13%)
Under similar conditions the chiral 2-methylene \( \gamma \)-lactam \( 5^{16} \) reacted with the ylide \( 8a \) (\( X = \text{OEt} \)) to produce three cycloadducts, \( 11 \), \( 12 \) and \( 13 \), in a ratio of 63 : 17 : 30, respectively, from \( ^1\text{H} \) 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 \textit{anti} to the ethyl ester substituent (\textit{via} transition state \( A \), \( R = \text{CO}_2\text{Et}, X = \text{OEt} \), Scheme 3).
Treatment of ethyl 2-(2-nitrophenyl)propenoate 6 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 (1S)-chiral sultam,18 was examined (Scheme 5). This reaction produced a 3.3 : 1 mixture of the diasteromeric 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 (1S)-configuration of the cyclopentane ring of 16 ([α]D26 −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 1R-configuration to this ring of the minor diastereomer 17 ([α]D24 +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\textsuperscript{a}

\begin{align*}
\text{CO}_{2}\text{Me} & \quad \text{NO}_2 \\
\text{PhH, RT} & \quad \text{CO}_{2}\text{Me} \\
\text{Bu}_3\text{P (0.1 equiv.)} & \quad \text{Me} \equiv \text{CO}_X\text{c} \\
\text{PhH, RT} & \quad \text{(66\% total yield)} \\
\quad & \quad \text{CO}_X\text{c} \\
\text{CO}_{2}\text{Me} & \quad \text{CO}_{2}\text{Me} \\
\text{NO}_2 & \quad \text{NO}_2 \\
\quad & \quad \text{(S)-16} \\
\quad & \quad [\text{X-ray}] \\
\quad & \quad \text{(R)-17} \\
\quad & \quad \text{(S)-18} \\
\quad & \quad \text{(R)-19} \\
\quad & \quad \text{(S)-20} \\
\quad & \quad \text{(R)-21} \\
\end{align*}

\textit{X}_c = \begin{tikzpicture}[scale=0.5]
\draw (0,0) circle (1);
\draw (-0.5,0) -- (0.5,0);
\draw (0,-1) -- (0,1);
\draw (0,0) -- (0.5,0.5);
\draw (0,0) -- (0.5,-0.5);
\draw (0,0) -- (-0.5,0.5);
\draw (0,0) -- (-0.5,-0.5);
\draw (0,0) -- (0.5,1);
\draw (0,0) -- (0.5,-1);
\draw (0,0) -- (-0.5,1);
\draw (0,0) -- (-0.5,-1);
\draw (0,0) -- (1,0);
\draw (0,0) -- (-1,0);
\draw (0,0) -- (0,1);
\draw (0,0) -- (0,-1);
\end{tikzpicture}

\textsuperscript{a} Reagents and conditions: (a) Sm(OTf)\textsubscript{3} (1 equiv), MeOH, 50°C, 18 h, 67\% ((S)-18), 68\% ((R)-19); (b) Zn dust (24 equiv), 8.9M HCl, MeOH/H\textsubscript{2}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). 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 and 31a, respectively, through amide bond formation between their respective carboxylic acids, 24 and 30 and aniline and 4-dimethylaminoaniline (Scheme 6). Amide 27 was obtained from the coupling reaction of aniline and the carboxylic acid 26 obtained from base catalysed hydrolysis of ester 22.

**Scheme 6**

(all compounds are racemic)

\[
\begin{align*}
\text{N} & \quad \text{O} \\
\text{Boc} & \quad \text{CO}_2\text{Et} \\
\text{9} & \quad \text{a} \quad \text{NH} \\
\text{22*} & \quad \text{b} \quad \text{O} \\
\text{CO}_2\text{Et} & \quad \text{CO}_2\text{Et} \\
\text{23} & \quad \text{R} = \text{Bn}, \text{X} = \text{OEt} \\
\text{24} & \quad \text{R} = \text{Bn}, \text{X} = \text{OH} \\
\text{25*} & \quad \text{R} = \text{Bn}, \text{X} = \text{NHAr} \\
\text{26} & \quad \text{R} = \text{H}, \text{X} = \text{OH} \\
\text{27} & \quad \text{R} = \text{H}, \text{X} = \text{NPh} \\
\text{22} & \quad \text{CO}_2\text{Et} \\
\text{10} & \quad \text{a} \quad \text{NH} \\
\text{28*} & \quad \text{b} \quad \text{O} \\
\text{CO}_2\text{Et} & \quad \text{CO}_2\text{Et} \\
\text{29} & \quad \text{R} = \text{Bn}, \text{X} = \text{OEt} \\
\text{30*} & \quad \text{R} = \text{Bn}, \text{X} = \text{OH} \\
\text{31*} & \quad \text{R} = \text{Bn}, \text{X} = \text{NPh} \\
\end{align*}
\]

\(a; \text{Ar} = \text{Ph}, b; \text{Ar} = 4-\text{Me}_2\text{NC}_6\text{H}_4^-\)

* Structure confirmed by X-ray

*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).

\textbf{Scheme 7}^a (all compounds are racemic)

\[ \text{CO}_2\text{Et} \xrightarrow{\text{a}} \text{CONHAr} \]

\( a; \text{Ar} = \text{Ph}, \ b; \text{Ar} = 4-\text{Me}_2\text{NC}_6\text{H}_4^- \)

\textit{Reagents and conditions:} (a) K$_2$CO$_3$ (2 equiv), MeOH/H$_2$O, 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 \(\gamma\)-lactam 4 and acrylate 6 with the ylide 8 (X = NHPh), that was generated \textit{in situ} from the reaction of N-phenyl 2-butynamide 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 \textit{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-butynamides has not been previously reported.

Scheme 8a (all compounds are racemic)

\[ \text{Reagents and conditions: (a) Anisole (10 equiv), TFA (125 equiv), DCM, 15 h, 57\%.} \]
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 $^1$H NMR spectrum of 42 showed two distinct N-H resonances ($\delta_H (C_6D_6)$ 7.96 (bs), 4.84 (bs)) and a deshielded aromatic proton ($\delta_H (C_6D_6)$ 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, \textit{via} 40, the spiro-cyclic ketones 41 and 42 (Scheme 10). We have not however attempted to isolate or characterize the intermediates involved.

\textbf{Scheme 10} (all compounds are racemic)
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 µM (5 mM drug stocks were prepared in DMSO. Cells were then exposed to 25 µM 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 µM for 33b against H460.

In conclusion, we have developed a new strategy for the synthesis of both racemic and enantiomerically enriched versions of the 2-azaspiro[4.4]nonan-1-one and spiro[cyclopentane-1,1’-[1H]isoindol]-3’(2H)-one ring systems using the phosphine-catalysed [3+2]-cycloaddition of both ester (7a) and amide derivatives (7c) of 2-butyroic acid. Enantiomerically enriched versions of 2 can be obtained using a chiral (1S)-camphor sultam derivative 7b of 2-butyroic 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 13C NMR (DEPT) spectra at 75 MHz in CDCl3 solution, unless otherwise noted. Abbreviations: PS (petroleum spirit, bp 40-60°C) and DCM (dichloromethane).

Ethyl (5S*) 2-(tert-butoxycarbonyl)-1-oxo-2-azaspiro[4.4]non-7-ene-7-carboxylate (9) and Ethyl (5R*) 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-butyroate (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 N2. 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%), Rf 0.78 (30% EtOAc:PS). 1H NMR (C6D6, 500 MHz) δ 6.37 (t, J 2 Hz, 1H, CH=), 3.98 (dd, J 14, 7.5 Hz, 2H, CH2CH3), 3.20
(ddd, J 13, 6, 6 Hz, 2H, NCH₃), 3.04 (dq, J 16.5, 2.5 Hz, 1H, CH-6β), 2.71 (dq, J 18.5, 2.5 Hz, 1H, CH-9β), 2.13 (d, 16.5 Hz, 1H, CH-6α), 1.73 (d, 18 Hz, 1H, CH-9α), 1.48 (s, 9H, (CH₃)₃), 1.12 (ddd, J 13, 6, 6 Hz, 1H, CH₂CH₃-4), 1.04 (ddd, J 13, 6, 6 Hz, 1H, CH₂CH₃-4), 0.97 (t, 7.5 Hz, 3H, CH₃). ¹³C NMR (CD₆D₆, 75 MHz) δ 175.4 (C-1), 163.7 (C=O₂Et), 151.0 (N=O₂), 139.8 (C=H), 134.3 (C-7), 82.1 (C(CH₃)₃), 60.1 (CH₂CH₃), 51.6 (C-5), 43.3 (CH₂-9), 42.9 (NCH₂), 42.3 (CH₂-6), 33.2 (CH₂-4), 28.1 (C(CH₃)₃), 14.3 (CH₃CH₂). MS (ES) m/z 348 ([M⁺+K⁺], 15%), 332.1 ([M⁺+Na⁺], 60%), 310.0 ([MH⁺], 32%), 254.1 ([MH⁺-C(CH₃)₃], 100%), 210.1 ([MH⁺-Boc], 85%); HRMS (ES) Calcd for C₁₆H₂₄NO₅ [MH⁺] 310.1654. Found: 310.1664. NMR data for 10 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. 107-110.5°C), Rₚ 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, CH₂CH₃), 3.90 (ddd, J 10.5, 8.5, 8.5 Hz, 1H, NCH₂CH₃), 2.62-2.69 (m, 1H, CH₆CH₃-8), 2.51-2.58 (m, 1H, CH₆CH₃-8), 2.38-2.46 (om, 2H, CH₆CH₃-9 and CH₆CH₃-4), 1.98 (ddd, J 13, 8.5, 4.5 Hz, 1H, CH₆CH₃-9), 1.92 (ddd, J 12.5, 8.5, 4 Hz, 1H, CH₆CH₃-4), 1.54 (s, 9H, (C(CH₃)₃), 1.26 (dt, J 7.5, 2.5 Hz, 3H, CH₃CH₂). ¹³C NMR δ 176.8 (C-1), 163.6 (CO₂Et), 150.6 (NCO₂), 147.5 (CH=), 138.0 (C-6), 83.0 (C(CH₃)₃), 60.8 (CH₂CH₃), 59.7 (C-5), 44.2 (NCH₂), 37.4 (CH₂-9), 31.7 (CH₂-8), 29.8 (CH₂-4), 28.4 (C(CH₃)₃), 14.5 (CH₃CH₂). MS (ES) m/z 310.2 ([MH⁺], 53%), 332.1 ([M⁺+Na⁺], 29%), 348.1 ([M⁺+K⁺], 23%), 254.1 ([MH⁺-C(CH₃)₃], 100%), 209.8 ([MH⁺-Boc], 95%); HRMS (ES) Calcd for C₁₆H₂₄NO₅ [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 (3S,5S)-1-oxo-2-azaspiro[4.4]non-7-ene-2,3,7-tricarboxylate (11) and 2-tert-butyl 3,7-diethyl (3S,5R)-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 N₂. 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%), \([\alpha]_D^{22} -17.5 (c 4.6, \text{CHCl}_3), R_f 0.57 (30\% \text{EtOAc:PS})\). 1H NMR (500 MHz) \(\delta 6.57 (s, 1H, \text{CH}=), 4.54 (dd, J 9.5, 4.5 Hz, 1H, \text{CH}-5), 4.21 (dq, J 6.5, 1.5 Hz, 2H, NCHCO\text{C}_2\text{H}_2), 4.16 (q, J 6.7 Hz, 2H, CCO\text{C}_2\text{H}_2), 3.15 (dd, J 16.5, 2 Hz, 1H, CH-6\beta), 3.04 (dd, J 18.5, 1.5 Hz, 1H, CH-9\beta), 2.55 (d, J 16.5 Hz, 1H, CH-6\alpha), 2.39 (d, J 17.5 Hz, 1H, CH-9\alpha), 2.33-2.55 (m, 1H, CH\text{A}_{\text{CHB}}-4), 2.09 (dd, J 13, 4 Hz, 1H, CH\text{B}\text{CH}_A-4), 1.49 (s, 9H, C(CH\text{3}_2)), 1.23-1.29 (m, 6H, CH\text{2CH}_2). \text{13C NMR} \delta 176.9 (\text{C}-1), 171.5 (\text{NCHCO}_2\text{Et}), 164.3 (\text{CCO}_2\text{Et}), 149.6 (\text{NCO}_2) 139.8 (\text{CH}=-), 134.4 (C-7), 84.0 (\text{(CH}_3)_3), 61.9 (\text{NCHCO}_2\text{CH}_2), 60.7 (\text{CCO}_2\text{CH}_2), 56.7 (\text{CH}-5), 51.0 (C-3), 45.2 (\text{CH}_2-9), 43.5 (\text{CH}_2-6), 37.9 (\text{CH}_2-4), 28.1 (\text{C(CH}_3)_3), 14.4 (\text{CH}_3\text{CH}_2), 14.3 (\text{CH}_3\text{CH}_2). \text{MS (ES) m/z 382.2 ([MH]^+), 5%}; \text{HRMS (ES) Caled for C}_{19}\text{H}_{28}\text{NO}_7 [\text{MH}^+] 382.1866. \text{Found: 382.1892. 13: A yellow oil (24 mg, 63 \mu\text{mol}, 13%), \([\alpha]_D^{23} -1.88 (c 0.14, \text{CHCl}_3), R_f 0.36 (30\% \text{EtOAc:PS})\). 1H NMR (500 MHz) \(\delta 6.65 (s, 1H, \text{CH}=-), 4.57 (dd, J 9.5, 3.5 Hz, 1H, \text{CH}-5), 4.21-4.29 (m, 2H, NCHCO\text{C}_2\text{H}_2), 4.18 (q, J 7.5 Hz, 2H, CCO\text{C}_2\text{H}_2), 3.12-3.17 (m, 1H, CH-6\beta), 3.08-3.12 (m, 1H, CH-9\beta), 2.51 (d, J 16.5 Hz, 1H, CH-6\alpha), 2.45 (d, J 18.5 Hz, 1H, CH-9\alpha), 2.33 (dd, J 13.5, 9.5 Hz, 1H, CH\text{A}_{\text{CHB}}-4), 2.20 (dd, J 13.5, 4 Hz, 1H, CH\text{B}\text{CH}_A-4), 1.51 (s, 9H, C(CH\text{3}_3)), 1.31 (t, J 7Hz, 3H, CCO\text{C}_2\text{CH}_2\text{CH}_3), 1.27 (t, J 7 Hz, 3H, NCHCO\text{C}_2\text{CH}_2\text{CH}_3). \text{13C NMR} \delta 177.0 (\text{C}-1), 171.1 (\text{NCHCO}_2\text{Et}), 164.3 (\text{CCO}_2\text{Et}), 149.4 (\text{NCO}_2), 139.9 (C-8), 133.8 (C-7), 83.8 (\text{(CH}_3)_3), 61.8 (\text{NCHCO}_2\text{CH}_2), 60.4 (\text{CCO}_2\text{CH}_2), 56.4 (\text{CH}-5), 50.7 (C-3), 44.8 (\text{CH}_2-9), 43.6 (\text{CH}_2-6), 37.8 (\text{CH}_2-4), 27.8 (\text{(CH}_3)_3), 14.2 (\text{CH}_3\text{CH}_2), 14.1 (\text{CH}_3\text{CH}_2). \text{MS (ES) m/z 382.2 ([MH]^+), 5%}; \text{HRMS (ES) Caled for C}_{19}\text{H}_{28}\text{NO}_7 [\text{MH}^+] 382.1866. \text{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). $^1$H NMR $\delta$ 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, $J$ 7.8 Hz, 1H, ArH-6), 6.74 (t, $J$ 1.8 Hz, 1H, CH=), 4.20 (q, $J$ 6.9 Hz, 2H, CH$_2$CH$_3$), 3.64 (s, 3H, CO$_2$CH$_3$), 3.62 (dq, $J$ 19.2, 2.7 Hz, 1H, CH-5$\alpha$), 3.52 (dq, $J$ 17.4, 2.5 Hz, 1H, CH-2$\alpha$), 3.21 (dm, $J$ 17.1 Hz, 1H, CH-2$\beta$), 2.99 (dt, $J$ 19.2, 2.4 Hz, 1H, CH-5$\beta$), 1.29 (t, $J$ 6.9 Hz, 3H, CH$_3$CH$_2$). $^{13}$C NMR $\delta$ 174.0 (C O$_2$Me), 164.0 (C O$_2$Et), 148.1 (ArC-2), 140.1 (CH=), 138.1 (ArC-1), 133.8 (C-3$'$), 133.2 (ArC-H-5), 128.3 (ArC-H-6), 128.0 (ArC-H-4), 125.3 (ArC-H-3), 60.6 (CH$_2$CH$_3$), 55.6 (C-1$'$), 52.4 (CO$_2$CH$_3$), 45.8 (CH$_2$-5$'$), 44.2 (CH$_2$-2$'$), 14.2 (CH$_2$CH$_3$). MS (Cl) m/z C$_{16}$H$_{18}$NO$_6$ 320 ([MH$^+$], 100%), 288 ([MH$^+$ - Et], 41%), 206 (68%), 246 (22%), 188 (21%); HRMS (Cl) Caled for C$_{16}$H$_{18}$NO$_6$ [MH$^+$] 320.1134. Found: 320.1132.

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

To a solution of 14 (29.5 mg, 0.092 mmol) in EtOH (0.7 mL) and H$_2$O (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 H$_2$O. The filtrate was then extracted with EtOAc and the organic extracts were combined and dried over MgSO$_4$ to yield a creamy brown oil (23.4 mg, 0.091 mmol, 98%), R$_f$ 0.5 (50% EtOAc:PS). $^1$H NMR (500 MHz) $\delta$ 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, $J$ 7Hz, 2H, CH$_2$CH$_3$), 3.27 (dd, $J$ 16.5, 2.5 Hz, 1H, CH-2$\alpha$), 3.19 (dd, $J$ 18.7, 2.25 Hz, 1H, CH-5$\alpha$), 2.90 (d, $J$ 16.5 Hz, 1H, CH-2$\beta$), 2.80 (d, $J$ 18.5 Hz, 1H, CH-5$\beta$), 1.31 (t, $J$ 7.25 Hz, 3H, CH$_3$CH$_2$). $^{13}$C NMR
δ 183.2 (C-2), 164.2 (CO₂Et), 140.6 (CH=), 139.7 (C-7a), 136.6 (C-3a), 134.8 (C-3’), 128.1 (ArCH₆), 123.0 (ArCH₅), 122.1 (ArCH₄), 109.9 (ArCH₇), 60.5 (CH₂CH₃), 52.5 (C-3), 44.9 (CH₂-5’), 43.4 (CH₂-2’), 14.2 (CH₃CH₂). MS (CI) m/z 258 ([MH+], 100%), 212 ([M+-OEt], 12%), 184 ([M+-CO₂Et], 12%); HRMS (EI) Calcd for C₁₅H₁₅NO₃ [M+] 257.1052. Found: 257.1048.

(3aS,6R,7aR,4’S)-Hexahydro-4’-methoxycarbonyl-4’-(2’’-nitrophenyl)-1’-(cyclopenten-1’-ylcarbonyl)-8,8-dimethyl-2,2-dioxide-3H-3a,6-methano-2,1-benzisothiazole ((S)-16) and (3aS,6R,7aR,4’R)-Hexahydro-4’-methoxycarbonyl-4’-(2’’-nitrophenyl)-1’-(cyclopenten-1’-ylcarbonyl)-8,8-dimethyl-2,2-dioxide-3H-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 N₂ 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 °C, [α]D²⁶ -22.0 (c 0.3, CHCl₃), Rf 0.53 (30% EtOAc:PS). ¹H NMR (500 MHz) δ 7.94 (d, J 7.5 Hz, 1H, ArH-3’’), 7.56 (bs, 2H, ArH-5’’, ArH-6’’), 7.41 (bs, 1H, ArH-4’’), 6.74 (bs, 1H, CH=), 4.07 (t, J 5.5 Hz, 1H, CH-7a), 3.74 (d, J 19.5 Hz, 1H, CH-7β), 3.66 (s, 3H, CO₂CH₃), 3.64 (d, J 19.0 Hz, 1H, CH-5’’), 3.45 (ABq, J 13.5 Hz, 2H, CH₂-3’’), 3.19 (d, J 19.0 Hz, 1H, CH-5’’), 3.06 (d, J 19.5 Hz, 1H, CH-3’’), 2.09-1.99 (m, 2H, CH-7α, CH-7β), 1.97-1.91 (m, 3H, CH-4β, CH-5β, CH-6), 1.44-1.37 (m, 2H, CH-4α, CH-5α), 1.24 (s, 3H, CH₃-9), 1.00 (s, 3H, CH₃-10). ¹³C NMR (125 MHz) δ 174.8 (CO₂Me), 171.3 (=CCO), 148.5 (ArC-2’’), 141.6 (CH=), 138.4 (ArC-1’’), 133.4 (ArCH-5’’), 129.2 (ArCH-6’’), 128.0 (ArCH-4’’), 125.1 (ArCH-3’’), 65.6 (CH-7a), 54.6 (C-4’’), 53.7 (CH₂-3), 52.4 (CO₂CH₃), 48.1
(C-3a), 47.7 (C-8), 47.0 (C_H2-3'), 45.5 (C_H2-5'), 45.2 (C_H-6), 38.3 (C_H2-7), 33.3 (C_H2-4), 26.5 (C_H2-5), 21.3 (C_H2-3'), 19.9 (C_H-6), 17.0 (C_H3-9), 19.9 (C_H3-10). LRMS (EI) m/z 488 ([M^+], 5%); HRMS (CI) Calcd for C_{24}H_{29}N_{2}O_{7}S [MH^+] 489.1695. Found: 489.1690. (R)-17: A colourless crystal, mp. 198-202 °C, [α]_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, ArH-3'), 7.60 (t, J 7.5 Hz, 1H, ArH-5'), 7.54(d, J 8.0 Hz, 1H, ArH-6'), 7.43 (t, J 7.5 Hz, 1H, ArH4'), 6.66 (s, 1H, CH=), 4.07 (m, 1H, C_H-7a), 3.80 (d, J 19.0 Hz, 1H, CH-3'), 3.68 (s, 3H, CO_2CH_3), 3.50 (d, J 13.5 Hz, 1H, CH-3α), 3.46-3.42 (m, 3H, CH-5β, CH-5α, CH-3α), 2.97 (d, J 19.0 Hz, 1H, CH-3α), 2.06-2.00 (m, 2H, CH-7α, CH-7β), 1.98-1.90 (m, 3H, CH-4β, CH-5β, CH-6), 1.42 (m, 2H, CH-4α, CH-5α), 1.23 (s, 3H, CH_2-9), 1.00 (s, 3H, CH_2-10). ^13C NMR (125 MHz) δ 173.9 (C_O2Me), 165.7 (=CCO), 148.2 (ArC-2'), 139.9 (CH=), 138.1 (ArC-1'), 134.7 (C-1'), 133.3 (ArC_H-5'), 128.6 (ArC_H-6'), 128.0 (ArC_H-4'), 125.4 (ArC_H-3'), 65.5 (CH-7α), 55.9 (C-4'), 53.6 (CH-3), 52.5 (CO_2CH_3), 48.1 (C-3a), 47.7 (C-8), 46.3 (CH-2-3'), 44.8 (CH-2-5'), 45.2 (CH-6), 38.4 (CH-2-7), 33.2 (CH_2-4), 26.5 (CH-2-5), 21.3 (CH-3-9), 19.9 (CH_3-10). MS (EI) m/z 488 ([M^+], 2.6%); HRMS (CI) Calcd for C_{24}H_{29}N_{2}O_{7}S [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 Sm(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: [α]_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, ArH-3'), 7.59 (dt, J 7.5, 1.5 Hz, 1H, ArH-3'), 7.44 (dt, J 7.5, 1.5 Hz, 1H, ArH-4'), 7.42 (dd, J 7.8, 1.5 Hz, 1H, ArH-6'), 6.76 (m, 1H, CH=), 3.77 (s, 3H, =CCO_2CH_3), 3.67 (s, 3H, PhCCO_2CH_3), 3.62 (dddd, J 19.5,
5.1, 5.1, 2.7 Hz, 1H, CH-5α), 3.51 (dddd, J 17.4, 5.1, 5.1, 2.4 Hz 1H, CH-2α), 3.22 (dt, J 17.1, 1.5 Hz, 1H, CH-2β), 2.98 (ddddd, J 19.1, 2.4, 2.4, 0.9 Hz, 1H, CH-5β). 13C NMR (125 MHz) δ 174.0 (PhCO2Me), 164.4 (=CCO2Me), 148.2 (ArC-2’), 140.4 (CH=), 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 (PhCO2CH3), 51.7 (=CCO2CH3), 45.8 (CH2-5), 44.2 (CH2-2). MS (ES) m/z 306 ([MH+], 13%); HRMS (ES) Calcd for C15H16NO6 [MH+] 306.0978. Found: 306.0966.

Dimethyl (1R)-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: [α]D26+50.0 (c 0.7, CHCl3), Rf = 0.26 in 20% EtOAc:PS). MS (ES+ve) m/z 306 (26%) [MH+]; HRMS (ES+ve) Calcd for C15H16NO6 [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’-[3H]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%), [α]D24+40.8 (c 1.2, CHCl3), Rf 0.23 (30% EtOAc:PS). 1H NMR δ 8.73 (bs, 1H, 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, CH-4’), 3.79 (s, 3H, CH3), 3.26 (ddd, J 18.3, 5.1, 2.7, 2.4 Hz, 1H, CH-2’a), 3.20 (ddd,
$J$ 20.3, 5.1, 2.7, 2.4 Hz, 1H, CH-5$^\prime_\alpha$), 2.90 (ddd, $J$ 18.3, 2.4, 1.5 Hz, 1H, CH-2$^\prime_\beta$), 2.80 (m, 1H, CH-5$^\prime_\beta$). $^{13}$C NMR δ 182.9 (C-2), 164.6 (CO$_2$Me), 140.9 (CH=), 139.7 (C-7a), 136.5 (C-3a), 134.5 (C-3$'$), 128.1 (ArCH-6), 123.0 (ArCH-5), 122.2 (ArCH-4), 109.8 (ArCH-7), 52.5 (C-3), 51.7 (CH$_3$), 45.0 (CH$_2$-5$'$), 43.4 (CH$_2$-2$'$). MS (EI) $m/z$ 243 ([M$^+$], 11%); HRMS (ES) Calcd for C$_{14}$H$_{14}$NO$_3$ [MH$^+$] 244.0974. Found: 244.0966.

**Methyl (1'R)-2-Oxo-spiro[3'-cyclopentene-1',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%), [$\alpha$]$_D^{23}$ +57.4 (c 1.0, CHCl$_3$), R$_f$ 0.52 (30% EtOAc:PS). The $^1$H NMR spectrum of (R)-21 was identical to that of (S)-20. MS (EI) $m/z$ 243 ([M$^+$], 50%); HRMS (ES) Calcd for C$_{14}$H$_{14}$NO$_3$ [MH$^+$] 244.0974. Found: 244.0963.

**Ethyl (5S$^\ast$)-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). $^1$H 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$_2$CH$_3$), 3.35 (t, $J$ 7.1 Hz, 2H, NCH$_2$), 3.02 (od, $J$ 16.5 Hz, 2H, CH-6$_\beta$, CH-9$_\beta$), 2.59 (d, $J$ 15.9 Hz, 1H, CH-6$_\alpha$), 2.46 (d, $J$ 18.9 Hz, 1H, CH-9$_\alpha$), 2.14-2.16 (m, 2H, CH$_2$-4), 1.32 (t, $J$ 7.0 3H, CH$_2$CH$_3$). $^{13}$C NMR δ 182.35 (C-1), 164.65 (CO$_2$Et), 140.9 (CH=), 134.5 (C-7), 60.4 (CH$_2$CH$_3$), 49.4 (C-5), 43.5 (CH$_2$-9), 42.0 (CH$_2$-6), 39.5 (NCH$_2$), 37.8 (CH$_2$-4), 14.4 (CH$_2$CH$_3$). MS (CI) $m/z$ 210 ([MH$^+$], 100%); HRMS (CI) Calcd for C$_{11}$H$_{16}$NO$_3$ [MH$^+$] 210.1130. Found: 210.1132.
Ethyl (5S*)-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%), Rf 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, NCH₂CH₃Ph), 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-6β, CH-9β), 2.56 (d, J 15.3 Hz, 1H, CH-6α), 2.43 (d, J 18.9 Hz, 1H, CH-9α), 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 (Cl) m/z 300 ([MH⁺], 8%); HRMS (EI) Calcd for C₁₈H₂₁NO₃ [M⁺] 299.1521. Found: 299.1508.

(5S*)-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 %), Rf 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, NCH₃CH₂Ph), 3.17-3.23 (m, 2H, CH₂-3), 3.11 (ddd, J 18.3, 4.9, 2.2 Hz, 1H, CH-9β), 3.05 (d, J 16.5, 4.9, 2.2, 1H, CH-6β), 2.56 (d, J 17.1 Hz, 1H, CH-6α), 2.45 (d, J 18.6 Hz, 1H, CH-9α), 1.92-2.08 (m, 2H, CH₂-4). ¹³C NMR δ 178.1 (C-1), 168.8 (C=O₂H), 143.5 (CH=), 136.4 (C-7), 133.9 (ArC-i), 128.9 (ArCH-m), 128.2 (ArCH-o), 127.8 (ArCH-p), 50.7 (C-5), 47.4 (NCH₂Ph), 44.1 (CH₂-9), 44.0 (CH₂-3), 42.0 (CH₂-6), 35.6 (CH₂-4). MS (CI) m/z 272 ([M⁺], 100%); HRMS (CI) Calcd for C₁₆H₁₇NO₃ [M⁺] 271.1208. Found: 271.1123.

(55°)-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 H₂O 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, Rₜ 0.32 (60% EtOAc:PS).

¹H NMR ¹H NMR (500 MHz) δ 7.55 (d, J 8 Hz, 2H, ArH-o), 7.29-7.34 (m, 5H, ArH), 7.23 (d, J 7.5 Hz, 2H, ArH-m), 7.11 (t, J 7.25 Hz, 1H, ArH-p), 6.50 (s, 1H, CH=), 4.49 (ABq, J 14.5 Hz, 2H, NCH₂), 3.21 (q, J 7 Hz, 2H, CH₂-3), 3.15 (d, J 16 Hz, 1H, CH-6β), 3.08 (d, J 18 Hz, 1H, CH-9β), 2.68 (d, J 15 Hz, 1H, CH-6α), 2.49 (d, 18 Hz, 1H, CH-9α), 2.00-2.11 (m, 2H, CH₂-4). ¹³C NMR (125 MHz) δ 177.6 (C-1), 162.7 (CONHPh), 137.8 (ArC-i), 137.7 (C-7), 136.2 (ArC-i'), 135.0 (CH=), 128.8 (ArCH), 128.6 (ArCH-m), 127.9(ArCH), 127.5 (ArCH), 124.2 (ArCH-p), 119.9 (ArCH-o), 50.3 (C-5), 47.1 (NCH₂), 43.7 (CH₂-3 and CH₂-9), 42.4 (CH₂-6), 35.3 (CH₂-4). MS (CI) m/z 347 ([MH⁺], 80%); HRMS (CI) Calcd for C₂₂H₂₂N₂O₂ [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, $4.8 \times 10^{-4}$ mol) and NEt$_3$ (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). $^1$H NMR (C$_6$D$_6$, 500 MHz) $\delta$ 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`, 2H, 1H, CH-2`), 2.01-2.06 (m, 1H, CH-5`, 1.60 (dt, $J$ 13, 8.5 Hz, 1H, CH-5`), 1.37-1.43 (m, 1H, 1H, CH-5`). 13C NMR (C$_6$D$_6$, 125 MHz) $\delta$ 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 (CH$_2$-2`), 36.5 (CH$_2$-4`), 33.4 (CH$_2$-5`). MS (EI) m/z 201 ([M +], 67%), 145 ([M + -(CH$_2$)$_2$CO], 100%); HRMS (EI) Calcd for C$_{12}$H$_{12}$NO$_2$ [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). $^1$H NMR (C$_6$D$_6$, 500 MHz) $\delta$ 8.64 (d, $J$ 8Hz, 1H, ArH-7), 7.96 (bs, 1H, NH$_2$H$_2$), 7.08 (t, $J$ 8Hz, 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$_2$H$_2$), 2.37 (ddd, $J$ 18, 9, 9 Hz, 1H, CH-4`), 2.22 (d, $J$ 18.5 Hz, 1H, CH-2`), 2.01 (ddd, $J$ 18.5, 9, 6 Hz, 1H, CH-4`), 1.87 (d, $J$ 18.5 Hz, 1H, CH-2`), 1.68-1.74 (m, 1H, 1H, CH-5`), 1.37-1.43 (m, 1H, 1H, CH-5`). 13C NMR (C$_6$D$_6$, 125 MHz) $\delta$ 212.5 (C-3`), 182.0 (C-2), 152.1 (CONH$_2$), 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 (CH$_2$-2`), 36.1 (CH$_2$-4`), 34.0 (CH$_2$-5`). LRMS (EI) m/z 244 ([M$^+$], 2%), 201 ([M$^+$ -CONH$_2$], 36%); HRMS (EI) Calcd for C$_{13}$H$_{12}$N$_2$O$_3$ [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%), R₇₀.28 (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 7.5 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’ₜ), 2.51 (dd, J 13, 10 Hz, 1H, CH-2’ₜ), 2.28-2.40 (m, 3H, CH₂-4’ and CH-5’ₜ), 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 (C O₂Et), 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%), R₇₀.38 (30% EtOAc:PS). 1H NMR (C₆D₆, 500 MHz) δ 8.14 (bs, 1H, NH), 7.22 (d, 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 7 Hz, 2H, CH₂CH₃), 3.38 (ddd, J 16, 16, 8 Hz, 1H, CH-3’ₜ), 2.43 (dd, J 13.5, 8.5 Hz, 1H, CH-2’ₜ), 2.33-2.38 (m, 1H, CH-4’ₜ), 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’ᵦ) 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 (C O₂Et), 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’ᵦ), 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.
5. References


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


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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 MoKα radiation source (λ = 0.71073 Å) (Exception: 28, which employed synchrotron radiation, λ = 0.5500 Å), N\textsubscript{t}(otal) reflections merging to N unique (R\textsubscript{int} cited) after 'empirical'/multiscan absorption correction (proprietary software), N\textsubscript{o} with F > 4σ(F) considered 'observed' and used in the full matrix least squares refinement (reflection weights: \(\sigma^2(F) + 0.00 \times n_w \times F^2\))\(^{-1}\). 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. C\textsubscript{16}H\textsubscript{23}NO\textsubscript{5}, \(M = 309.4\). Triclinic, space group \(\text{P}\overline{1} \) (#2), \(a = 6.085(1), b = 9.534(2), c = 14.682(2) \text{ Å}, \alpha = 79.674(3), \beta = 80.484(3), \gamma = 77.536(3)\). \(V = 811.0 \text{ Å}^3\). \(D_c (Z = 2) = 1.267 \text{ g cm}^{-3}\). \(\mu_{\text{Mo}} = 0.09 \text{ mm}^{-1}\); specimen: 0.27 x 0.20 x 0.12 mm; \(T\)\textsubscript{ca.} 153 K. (\(S\))-16. C\textsubscript{24}H\textsubscript{28}N\textsubscript{2}O\textsubscript{7}S, \(M = 488.6\). Monoclinic, space group \(P2_1 \) (#4), \(a = 12.085(5), b = 7.243(1), c = 13.924(2) \text{ Å}, \beta = 101.040(3)\). \(V = 1196 \text{ Å}^3\). \(D_c (Z = 2) = 1.356 \text{ g cm}^{-3}\). \(\mu_{\text{Mo}} = 0.18 \text{ mm}^{-1}\); specimen: 0.28 x 0.18 x 0.14 mm; \(T\)\textsubscript{min/max} = 0.76. 2θ\textsubscript{max} = 58°; N\textsubscript{t} = 7868, N = 3938 (R\textsubscript{int} = 0.025), N\textsubscript{o} = 2934; R = 0.047, R\textsubscript{w} = 0.052 (n\textsubscript{w} = 0.4). |\(\Delta \rho_{\text{max}}\)| = 0.34(3) e Å\(^{-3}\). (x,y,z,\(U_{\text{iso}}\))\textsubscript{H} refined. \(T\)\textsubscript{ca.} 153 K. (\(S\))-16. C\textsubscript{24}H\textsubscript{28}N\textsubscript{2}O\textsubscript{7}S, \(M = 488.6\). Monoclinic, space group \(P2_1 \) (#4), \(a = 12.085(5), b = 7.243(1), c = 13.924(2) \text{ Å}, \beta = 101.040(3)\). \(V = 1196 \text{ Å}^3\). \(D_c (Z = 2) = 1.356 \text{ g cm}^{-3}\). \(\mu_{\text{Mo}} = 0.18 \text{ mm}^{-1}\); specimen: 0.28 x 0.18 x 0.14 mm; \(T\)\textsubscript{min/max} = 0.89.
$2\theta_{\text{max}} = 58^\circ$; $N_t = 11606$, $N = 3210$ ($R_{\text{int}} = 0.025$), $N_o = 2241$; $R = 0.053$, $R_w = 0.056$ ($n_w = 0.6$). 
$|\Delta \rho_{\text{max}}| = 0.28(3)$ e Å$^{-3}$. $x_{\text{abs}} = 0.06(16)$. 

$T$ ca. 300 K. **22.** $\text{C}_1\text{H}_{15}\text{NO}_3$, $M = 209.3$. Triclinic, space group $P\bar{1}$, $a = 5.597(1)$, $b = 7.910(2)$, $c = 12.861(3)$ Å, $\alpha = 86.683(5)$, $\beta = 79.353(5)$, $\gamma = 75.871(5)^\circ$, $V = 542.6\text{ Å}^3$. $D_c$ ($Z = 2$) = 1.28 \text{ g cm}^{-3}$. $\mu_{\text{Mo}} = 0.09 \text{ mm}^{-1}$; specimen: 0.63 x 0.12 x 0.08 mm; $T'_{\text{min/max}} = 0.78$. 

$2\theta_{\text{min}} = 58^\circ$; $N_t = 6707$, $N = 2861$ ($R_{\text{int}} = 0.027$), $N_o = 2274$; $R = 0.044$, $R_w = 0.051$ ($n_w = 0.3$). $|\Delta \rho_{\text{max}}| = 0.36(3)$ e Å$^{-3}$. 

$T$ ca. 153 K. **25a.** $\text{C}_{2}2\text{H}_{22}\text{N}_{2}\text{O}_{2}$, $M = 346.5$. Orthorhombic, space group $Pca2_1$ (#29), $a = 24.140(16)$, $b = 7.734(5)$, $c = 9.836(7)$ Å, $V = 1836 \text{ Å}^3$. 

$2\theta_{\text{max}} = 50^\circ$; $N_t = 13466$, $N = 1698$ ($R_{\text{int}} = 0.11$), $N_o = 1284$; $R = 0.066$, $R_w = 0.090$ ($n_w = 3$). $|\Delta \rho_{\text{max}}| = 0.30(6)$ e Å$^{-3}$. $x_{\text{abs}}$ 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 $P\bar{1}$, $a = 8.260(3)$, $b = 10.892(4)$, $c = 12.538(4)$ Å, $\alpha = 67.764(6)$, $\beta = 82.723(6)$, $\gamma = 81.564(6)^\circ$, $V = 1030 \text{ Å}^3$. $D_c$ ($Z = 2$) = 1.25 \text{ g cm}^{-3}$. $\mu_{\text{Mo}} = 0.08 \text{ mm}^{-1}$; specimen: 0.12 x 0.08 x 0.04 mm; $T'_{\text{min/max}} = 0.88$. 

$2\theta_{\text{min}} = 50^\circ$; $N_t = 9351$, $N = 3586$ ($R_{\text{int}} = 0.046$), $N_o = 2207$; $R = 0.057$, $R_w = 0.072$ ($n_w = 0.2$). $|\Delta \rho_{\text{max}}| = 0.32(4)$ e Å$^{-3}$. 

$T$ 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), $a = 8.204(2)$, $b = 18.128(5)$, $c = 8.914(2)$ Å, $\beta = 107.823(4)^\circ$, $V = 1262 \text{ Å}^3$. $D_c$ ($Z = 4$) = 1.34 g cm$^{-3}$. $\mu_{\text{Mo}} = 0.09 \text{ mm}^{-1}$; specimen: 0.12 x 0.08 x 0.08 mm; $T'_{\text{min/max}} = 0.92$. 

$2\theta_{\text{max}} = 50^\circ$; $N_t = 10582$, $N = 2207$ ($R_{\text{int}} = 0.065$), $N_o = 1747$; $R = 0.056$, $R_w = 0.081$ ($n_w = 2$). $|\Delta \rho_{\text{max}}| = 0.30(5)$ e Å$^{-3}$. 

$T$ ca. 153 K. **28.** $\text{C}_{11}\text{H}_{15}\text{NO}_3$, $M = 209.3$. Monoclinic, space group $P2_1/c$, $a = 14.2396(11)$, $b = 6.2065(5)$, $c = 11.9144(9)$ Å, $\beta = 102.276(4)^\circ$, $V = 1029 \text{ Å}^3$. $D_c$ ($Z = 4$) = 1.35 g cm$^{-3}$. $\mu_{\text{Mo}} = 0.06 \text{ mm}^{-1}$; specimen: not recorded; $T'_{\text{min/max}} = 1.00$. 

$2\theta_{\text{max}} = 45^\circ$; $N_t = 28315$, $N = 2908$ ($R_{\text{int}} = 0.97$), $N_o = 2306$; $R = 0.043$, $R_w = 0.052$ ($n_w = 0.8$). $|\Delta \rho_{\text{max}}| = 0.49(4)$ e Å$^{-3}$. (x,y,z,U$_{\text{iso}}$)$_{\text{H}}$ refined. 

$T$ ca. 120 K. **30.** $\text{C}_{16}\text{H}_{17}\text{NO}_3$, $M = 271.3$. Orthorhombic, space group $Pbc\text{a}$ (# 61), $a = 11.667(7)$, $b = 10.836(6)$, $c = 21.167(12)$ Å, $V = 2676 \text{ Å}^3$. $D_c$ ($Z = 8$) = 1.34 g cm$^{-3}$. $\mu_{\text{Mo}} = 0.09 \text{ mm}^{-1}$; specimen: 0.13 x 0.06 x 0.03 mm; $T'_{\text{min/max}} = 0.00$. 

$2\theta_{\text{max}} = 50^\circ$; $N_t = 20960$, $N = 2394$ ($R_{\text{int}} = 0.16$), $N_o = 975$; $R = 0.087$, $R_w = 0.011$ ($n_w = 4.5$). $|\Delta \rho_{\text{max}}| = 0.36(5)$ e Å$^{-3}$. 

*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 $P\bar{1}$, $a = 5.121(1)$, $b = 9.606(1)$, $c = 12.379(1)$ Å, $\alpha = 69.657(3)$, $\beta = 81.925(3)$, $\gamma = 90^\circ$.
74.622(3)°, \( V = 871.8 \, \text{Å}^3 \). \( D_c \) \((Z = 2) = 1.320 \, \text{g cm}^{-3}\). \( \mu_{\text{Mo}} = 0.09 \, \text{mm}^{-1} \); specimen: 0.25 x 0.22 x 0.04 mm; \( T'_{\text{min/max}} = 0.89 \). \( \theta_{\text{max}} = 65° \); \( N_t = 12099 \), \( N = 6128 \) \((R_{\text{int}} = 0.025)\), \( N_o = 4580 \); \( R = 0.055 \), \( R_w = 0.077 \) \((n_w = 3.5)\). \( |\Delta\rho_{\text{max}}| = 0.53(3) \, \text{e Å}^{-3} \). 41. \( \text{C}_{12}\text{H}_{11}\text{NO}_2 \), \( M = 201.2 \). Triclinic, space group \( \bar{P}1 \), \( a = 6.667(4) \), \( b = 10.528(6) \), \( c = 14.730(8) \, \text{Å} \), \( \alpha = 105.632(9) \), \( \beta = 98.876(10) \), \( \gamma = 90.305(10)° \), \( V = 983 \, \text{Å}^3 \). \( D_c \) \((Z = 4) = 1.360 \, \text{g cm}^{-3}\). \( \mu_{\text{Mo}} = 0.09 \, \text{mm}^{-1} \); specimen: 0.13 x 0.11 x 0.03 mm; \( T'_{\text{min/max}} = 0.74 \). \( \theta_{\text{max}} = 50° \); \( N_t = 9300 \), \( N = 3355 \) \((R_{\text{int}} = 0.25)\), \( N_o = 1645 \); \( R = 0.12 \), \( R_w = 0.25 \) \((n_w = 2.5)\). \( |\Delta\rho_{\text{max}}| = 1.2(2) \, \text{e Å}^{-3} \).  Comment. The conformations of the two C₅ 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 \( P2_1/n \) \(#14\), \( a = 16.203(3) \), \( b = 6.373(3) \), \( c = 29.233(2) \, \text{Å} \), \( \beta = 90.207(7)° \), \( V = 1156 \, \text{Å}^3 \). \( D_c \) \((Z = 4) = 1.404 \, \text{g cm}^{-3}\). \( \mu_{\text{Mo}} = 0.10 \, \text{mm}^{-1} \); specimen: 0.50 x 0.10 x 0.04 mm; \( T'_{\text{min/max}} = 0.89 \). \( \theta_{\text{max}} = 52° \); \( N_t = 7690 \), \( N = 2009 \) \((R_{\text{int}} = 0.043)\), \( N_o = 1528 \); \( R = 0.059 \), \( R_w = 0.096 \) \((n_w = 6)\). \( |\Delta\rho_{\text{max}}| = 0.62(4) \, \text{e Å}^{-3} \).  \( T \text{ ca.} 153 \, \text{K} \).
Experimental procedures for the synthesis of compounds 25b-37

(5S\textsuperscript{\textcircled{\textdegree}})-2-Benzyl-1-oxo-\textit{N-(o)}-\textit{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 \textit{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 N\textsubscript{2} 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\textdegree C, R\textsubscript{f} 0.30 (70% EtOAc:PS). \textsuperscript{1}H NMR (500 MHz) \(\delta\) 7.39 (d, \(J\) 8.5 Hz, 2H, ArH-\textit{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\textsubscript{2}CH\textsubscript{2}Ph), 3.20 (q, \(J\) 6.3 Hz, 2H, CH\textsubscript{2}-3), 3.14 (dd, \(J\) 15.5, 2.5 Hz, 1H, CH-6\textit{p}), 3.08 (dd, \(J\) 18, 2.5 Hz, 1H, CH-9\textit{p}), 2.92 (bs, 6H, N(CH\textsubscript{3})\textsubscript{2}), 2.66 (d, \(J\) 15.5 Hz, 1H, CH-6\textit{a}), 2.47 (d, \(J\) 17.5 Hz, 1H, CH-9\textit{a}), 2.10-1.99 (m, 2H, CH\textsubscript{2}-4). \textsuperscript{13}C NMR \(\delta\) 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 (NCH\textsubscript{2}Ph), 43.9 (CH\textsubscript{2}-3), 43.8 (CH\textsubscript{2}-9), 42.6 (CH\textsubscript{2}-6), 41.1 (N(CH\textsubscript{3})\textsubscript{2}), 35.5 (CH\textsubscript{2}-4). MS (Cl) \textit{m/z} 390 ([MH\textsuperscript{+}], 100%); HRMS (Cl) Calcd for C\textsubscript{24}H\textsubscript{28}N\textsubscript{3}O\textsubscript{2} [MH\textsuperscript{+}] 390.2181. Found: 390.2170.

(5S\textsuperscript{\textcircled{\textdegree}})-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\textdegree C, \(R_f\) 0.03 (EtOAc). \textsuperscript{1}H NMR \(\delta\) 6.79 (bs, 1H, NH), 6.68 (s, 1H, CH=), 3.68-3.76 (m, 2H, NCH\textsubscript{2}), 3.03 (overlapping d, \(J\) 14.4 Hz, 2H, CH-6\textit{p}, CH-9\textit{p}), 2.59 (d, \(J\) 15 Hz, 1H, CH-6\textit{a}), 2.47 (d, \(J\) 18 Hz, 1H, CH-9\textit{a}), 2.04-2.21 (m, 2H, CH\textsubscript{2}-4). \textsuperscript{13}C NMR \(\delta\) 181.7 (C-1), 165.0 (CO\textsubscript{2}H), 141.2 (CH=), 134.1 (C-7), 49.4 (C-5), 43.7 (CH\textsubscript{2}-9), 42.1 (CH\textsubscript{2}-6), 39.5 (NCH\textsubscript{2}), 37.9
(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-6β), 3.05 (dd, J 18.1, 2.5 Hz, 1H, CH-9β), 2.71 (d, J 16.2 Hz, 1H, CH-6α), 2.52 (d, J 18.3 Hz, 1H, CH-9α), 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, CH₃CH₃), 3.50 (ddt, J 9.3, 3.6, 0.9 Hz, 2H, NCH₂CH₃), 3.35 (dt, J 9.3, 7.8 Hz, 1H,
**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%), Rf 0.42 (50% EtOAc:PS). \(^1\)H 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, NCH\(_2\)CH\(_2\)Ph), 4.08-4.23 (m, 2H, CH\(_2\)CH\(_3\)), 3.35 (dt, J 9.4, 3.9 Hz, 1H, CH\(_2\)CH\(_2\)-3), 3.21 (dd, J 9.3, 8.4, 6.9 Hz, 1H, CH\(_2\)CH\(_2\)-3), 2.61-2.73 (m, 1H, CH\(_2\)CH\(_2\)-8), 2.55 (dd, J 8.7, 6.3, 2.4 Hz, 1H, CH\(_2\)CH\(_2\)-8), 2.33-2.46 (om, 2H, CH\(_2\)CH\(_2\)-9 and CH\(_2\)CH\(_2\)-4), 1.89-2.00 (m, 2H, CH\(_2\)CH\(_2\)-9 and CH\(_2\)CH\(_2\)-4), 1.22-1.29 (m, 3H, CH\(_2\)CH\(_3\)). \(^{13}\)C NMR δ 176.9 (C-1), 163.8 (CO\(_2\)Et), 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\(_2\)CH\(_3\)), 56.7 (C-5), 47.0 (NCH\(_2\)Ph), 44.2 (CH\(_2\)-3), 36.9 (CH\(_2\)-9), 31.2 (CH\(_2\)-8), 30.5 (CH\(_2\)-4), 14.1 (CH\(_2\)CH\(_3\)). MS (CI) m/z 300 ([MH\(^+\)], 8%); HRMS (EI) Calcd for C\(_{18}\)H\(_{21}\)NO\(_3\) [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. \(^1\)H NMR (CD\(_3\)OD, 500 MHz) δ 7.25-7.34 (m, 5H, ArH), 6.99 (t, J 2.5 Hz, 1H,
CH=), 4.48 (ABq, $J$ 14.7 Hz, 2H, NCH$_A$CH$_B$Ph), 3.25-3.39 (m, 2H, CH$_2$-3), 2.59 (dt, $J$ 7.25, 2.5 Hz, 1H, CH$_2$-8), 2.37 (ddd, $J$ 13, 9, 8 Hz, 1H, CH$_A$CH$_B$-4), 2.28 (ddd, $J$ 12.5, 8.75, 8.5 Hz, 1H, CH$_A$CH$_B$-9), 2.00-2.08 (m, 2H, CH$_B$CH$_A$-9 and CH$_B$CH$_A$-4). $^{13}$C NMR (CD$_3$OD, 125 MHz) δ 180.0 (C-1), 167.7 (CO$_2$H), 148.6 (CH=), 137.6 (C-7), 139.9 (ArC-i), 129.7 (ArCH-m), 128.9 (ArCH-o), 128.6 (ArCH-p), 58.8 (C-5), 47.8 (NCH$_2$Ph), 45.6 (CH$_2$-3), 37.3 (CH$_2$-9), 32.1 (CH$_2$-8), 31.4 (CH$_2$-4). MS (Cl) $m/z$ 272 ([MH$^+$], 100%); HRMS (Cl) Calcd for C$_{16}$H$_{17}$NO$_3$ [M$^+$] 271.1208. Found: 271.1123.

(5R')-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). $^1$H NMR δ 8.38 (bs, 1H, NH), 7.52 (d, $J$ 7.5 Hz, 2H, ArH-o'), 7.24-7.29 (m, 7H, ArH), 7.06 (t, $J$ 7.35 Hz, 1H, ArH-p), 6.68 (bs, 1H, CH=), 4.53 (ABq, $J$ 14.7 Hz, 2H, NCH$_A$CH$_B$Ph), 3.39 (dt, $J$ 9.3, 3 Hz, 1H, CH$_A$CH$_B$-3), 3.24 (dd, $J$ 17.4, 7.8 Hz, 1H, CH$_B$CH$_A$-3), 2.54-2.62 (m, 2H, CH$_2$-8), 2.49 (dt, $J$ 12, 8.4 Hz, 1H, CH$_A$CH$_B$-4), 2.34 (ddd, 12.6, 9, 8.1 Hz, 1H, CH$_A$CH$_B$-9), 1.93-2.01 (om, 2H, CH$_B$CH$_A$-9 and CH$_B$CH$_A$-4). $^{13}$C NMR δ 177.9 (C-1), 163.6 (CONHPh), 142.4 (C-7), 139.9 (CH=), 138.3 (ArC-i'), 136.5 (ArC-i), 129.0 (ArCH), 128.9 (ArCH), 128.1 (ArCH), 127.7 (ArCH-p), 124.2 (ArCH-p'), 120.2 (ArCH-o'), 58.8 (C-5), 47.4 (NCH$_2$Ph), 44.7 (CH$_2$-3), 36.4 (CH$_2$-9), 31.3 (CH$_2$-8), 30.7 (CH$_2$-4). MS (Cl) $m/z$ 347 ([MH$^+$], 57%), 346 ([M$^+$], 26%), 225 ([M$^+$-CONHPh], 17%), 149 ([M$^+$-CONHPh, Ph], 45%); HRMS (Cl) Calcd for C$_{22}$H$_{22}$N$_2$O$_3$ [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, R₇ 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 7.5Hz, 1H, ArH-7), 3.28 (dd, d 16.5, 2.7 Hz, 1H, CH-2’α), 3.22 (dd, J 16.5 Hz, 2.1Hz, 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, R₇ 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 x 10⁻⁵ mol, 52%), mp. 184°C. ¹H NMR δ 8.87 (bs, 1H, NH), 7.78 (bs, 1H, CONHPh), 7.58 (d, J 8.1Hz, 2H, ArH-0), 7.32 (t, J 7.8Hz, 2H, ArH-m), 7.24 (d, J 7.8Hz, 1H, ArH-4), 7.20 (t, J 7.2Hz, 1H, ArH-6), 7.10 (t, J 7.5Hz, 1H, ArH-p), 7.01 (t, J 7.6Hz, 1H, ArH-5),
6.91 (d, J 7.8Hz, 1H, ArH-7), 6.68 (s, 1H, CH=), 3.32 (dd, J 16, 2.1Hz, 1H, CH-2’α), 3.18 (d, J 18.3, 2.1Hz, 1H, CH-5’α), 3.00 (d, J 16.2Hz, 1H, CH-2’β), 2.82 (d, J 18Hz, 1H, CH-5’β). 13C NMR δ 182.9 (C-2), 162.5 (CONH), 139.7 (C-7a), 138.2 (C-3’), 137.6 (ArC-β), 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%), Rf 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). 13C NMR δ 182.6 (C-2), 162.1 (=C=O), 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-β), 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, Ar H-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, NCH3), 3.77 (s, 3H, OCH3), 1.70 (s, 3H, CCH3). 13C 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=CH3), 74.1 (C=CH3), 55.0 (OCH3), 51.5 (NCH3), 3.68(CCH3). MS (ES) m/z 280.2 ([M+H]+, 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%), Rf 0.59 (50% EtOAc:PS). 1H NMR (500 MHz) δ 7.22-7.33 (m, 3H, Ar H-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, NCH3), 3.77 (s, 3H, OCH3), 3.50-3.58 (m, 2H, CH2-3), 2.74 (d, J 18 Hz, 1H, CH-9β), 2.73 (d, J 14.7 Hz, 1H, CH-6β), 2.26 (d, J 14.4 Hz, 1H, CH-6α), 2.18 (d, J 18.3 Hz, 1H, CH-9α), 1.71-173 (m, 2H, CH2-4), 1.52 (s, 9H, C(CH3)3). 13C 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 (NCH3), 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+]}
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 2 d. 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 (C_6D_6, 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-o’), 6.67 (t, J 7.7 Hz, 1H, ArH-4), 5.44 (s, 1H, CH=), 4.94 (ABq, J 14.5 Hz, 2H, NCH_2), 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, CO_2CH_3 and OCH_3), 3.18 (d, J 17.5 Hz, 1H, CH-2’β), 2.45 (d, J 18.5 Hz, 1H, CH-5’β). 13C NMR (C_6D_6, 125 MHz) δ 173.8 (C=O2Me), 165.7 (C=ON), 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 (CO_2CH_3), 53.1 (NCH_2), 51.9 (OCH_3), 47.0 (CH_2-2’), 45.9 (CH_2-5’). MS (ES) m/z 487 (15%) [MH^+], 455 (18%) [M^+ - OMe]; HRMS (ES) Calcd for C_{28}H_{33}N_2O_5 [MH^+] 477.2389. Found: 477.2412.

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. Na_2CO_3 solution and then extracted with EtOAc to yield 37 as a brown oil (12.4
mg, 0.029 mmol, 16%, Rf = 0.63 in 70% EtOAc:PS). \( ^1 \)H NMR (C\(_6\)D\(_6\), 500 MHz) \( \delta \) 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\( ^{\prime} \)), 6.43 (d, \( J \) 8 Hz, 1H, ArH-7), 5.69 (s, 1H, CH=), 4.95 (ABq, \( J \) 14 Hz, 2H, NCH\(_2\)), 3.29 (s, 3H, OCH\(_3\)), 3.23 (dd, \( J \) 16, 2.5 Hz, 1H, CH-2\( ^{\prime} \)), 2.88 (dd, \( J \) 18, 2.5 Hz, 1H, CH-5\( ^{\prime} \)), 2.71 (d, \( J \) 16.5 Hz, 1H, CH-2\( ^{\prime} \)), 2.18 (d, \( J \) 17.5 Hz, 1H, CH-5\( ^{\prime} \)). \( ^{13} \)C NMR (C\(_6\)D\(_6\), 125 MHz) \( \delta \) 182.0 (C-2), 165.9 (CON), 159.5 (ArC-\( p \)), 143.4 (ArC-i), 140.4 (C-7a), 138.3 (C-3\( ^{\prime} \)), 137.1 (C-3a), 135.3 (CH=), 130.6 (ArCH-\( o \)), 130.3 (ArC-i\( ^{\prime} \)), 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\( ^{\prime} \)), 109.6 (ArCH-7), 54.6 (CH\(_3\)), 53.1 (NCH\(_2\)), 52.5 (C-3), 46.0 (CH\(_2\)-2\( ^{\prime} \)), 44.8 (CH\(_2\)-5). MS (Cl) \( m/z \) 425 ([MH\(^{+}\)], 37%); HRMS (El) Calcd for C\(_{27}\)H\(_{24}\)N\(_2\)O\(_3\) [M\(^{+}\)] 424.1787. Found: 424.1786.