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Application of copper(II)-mediated radical cross-dehydrogenative coupling to prepare spirocyclic oxindoles and to a formal total synthesis of Satavaptan[‡]

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ABSTRACT

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Keywords: copper cross-dehydrogenative coupling total synthesis analogue synthesis vasopressin antagonists Application of radical cross-dehydrogenative coupling (CDC) procedures to prepare a range of novel spirocyclic oxindoles and to a formal total synthesis of the vasopressin V_2 receptor antagonist Satavaptan is reported. The key step involves a copper-mediated oxidative cyclisation of a simple linear anilide precursor to give the spirocyclic oxindole core. This synthetic approach was also used to prepare novel Satavaptan scaffolds and analogues.

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Tetrahedron

1. Introduction

Hyponatremia, or low blood sodium levels, is a common complication in several diseases including congenital heart failure, cirrhosis of the liver, and syndrome of inappropriate antidiuretic hormone (SIADH);¹ common diuretics typically used in the treatment of such diseases often lead to loss of essential sodium and potassium salts.² Several vasopressin V₂ receptor antagonists have been developed to address this problem (Figure 1). Selective vasopressin V₂ receptor antagonists (e.g. 1-3) work by blocking the production of vasopressin, an anti-diuretic hormone responsible for causing the kidneys to retain water. Thus, administration of Tolvaptan 2 alongside traditional diuretics has been shown to increase fluid excretion without causing hyponatremia in patients suffering from heart failure.³

Our interest concerned Satavaptan 1 and improved analogues. The synthesis of Satavaptan 1 was first reported by Sanofi in 1999 and involves formation of the oxindole core via a classical Fischer cyclisation under harsh conditions (180 °C reaction temperature), while tedious late-stage separation of the *syn-* and *anti-*stereoisomers was also required.⁴ These shortcomings were addressed in a subsequent synthesis by Liotta in 2001 (Scheme 1).⁵ Thus, in the Liotta synthesis, the key oxindole 6 was prepared via a Rh-catalysed annulation of diazo compound 5 at room temperature. Construction of the spirocyclic ketone 11 was



Figure 1. Examples of vasopressin V₂ receptor antagonists.

achieved through subsequent double alkylation with dibromide 10, itself prepared in 3 steps from methyl 3-



Scheme 1. Previous synthesis of Satavaptan and new approach via copper-mediated cross-dehydrogenative coupling

bromopropionate 7. Crucially, conditions were established for the *syn*-selective reduction of ketone **12** using L-Selectride as the hydride source, obviating the need for separation of a mixture of isomers at a later stage in the synthesis. The origin of this selectivity was proposed to be trapping of the cyclohexane in the twist-boat conformation via coordination of both carbonyl oxygen atoms to the lithium cation, thus revealing the correct face for hydridic attack. Alkylation of the cyclohexanol and removal of the benzyl protecting group under Birch conditions gave N-H oxindole **14**, which was treated with arylsulfonyl chloride **15** to deliver Satavaptan **1**. Several other formal syntheses of Satavaptan have also been reported, invoking either a radical⁶ or hypervalent iodine-mediated⁷ spirocyclisation, or alkylation/Dieckmann condensation⁸ as the key step.

We have previously reported the synthesis of oxindoles **17** through the intramolecular Cu(II)-catalysed radical crossdehydrogenative coupling (CDC) of simple anilides **16**, which proceeds via homolytic aromatic substitution of stabilised radical **18** (Scheme 1).^{9,10} A range of electron-withdrawing groups, including esters,^{9a} lactams^{9b} and ketones,^{9c-e} were well tolerated in this process. We now wish to report the application of this highly atom-economical approach to the preparation of Liotta's key spirocyclic oxindole intermediate 12, thus representing a new formal synthesis of Satavaptan. In our approach, the target molecule 12 would be derived by deoxygenation of selectively protected ketone 19, produced by the radical CDC cyclisation of anilide 20. This synthetic approach is also applied to prepare novel Satavaptan scaffolds and analogues (see later).

2. Results and Discussion

In order to establish the feasibility of preparing the key spirocyclic oxindole core of Satavaptan via our radical crossdehydrogenative coupling procedure, initial studies focused on the cyclisation of simple anilides **21** (Scheme 2).^{9c} In the event, treatment of linear precursors **21a-f** with inexpensive $Cu(OAc)_2$ ·H₂O in refluxing toluene under an atmosphere of O₂ delivered a range of spirocyclic oxindoles **22a-f** featuring 5-, 6-, and 7-membered ring ketones. Crucially, several different removable *N*-protecting groups (including Bn, DMB and PMB) were well-tolerated in this process. Furthermore, groups allowing for further functionalisation such as an alkene (**22e**) or epoxide



Scheme 2. Substrate scope in the copper-mediated synthesis of spirocyclic oxindoles.

(22f) were also successfully incorporated into the spirocyclic products. With conditions for the oxindole spirocyclisation in hand, a simple model system was next examined to establish the viability of the deoxygenation required for the formal synthesis of Satavaptan (Scheme 3). Synthesis of the model system began with selectively protected ketoester 23,¹¹ which was saponified to acid 24 in a two-step procedure involving first transesterification to the benzyl ester followed by hydrogenolysis.¹² Next, coupling of acid 24 with *N*-methylaniline in the presence of Mukaiyama's reagent delivered linear precursor 25 primed for the cross-dehydrogenative coupling. Rapid cyclisation occurred on



Scheme 3. Model system for the deoxygenation of spirocyclic oxindoles.

treatment of Panilide 25 with a catalytic quantity of $Cu(OAc)_2 \cdot 2H_2O$ in refluxing mesitylene to give spirocyclic oxindole 26 in 52% yield. To facilitate the carbonyl deoxygenation, ketone 26 was first reduced to the corresponding alcohol 27 in excellent yield. In the first instance, deoxygenation was successfully carried out using a classical Barton-McCombie reaction via the corresponding imidazole-1-thiocarbonyl derivative.¹³ However, an alternative route which negates the need for the use of highly toxic tin reagents was considered desirable. Thus, cleavage of the acetal and concomitant dehydration was achieved under acidic conditions to give enone 29, which could be hydrogenated to give the desired ketone 30 in high yield.

Having successfully established protocols for the key oxindole spirocyclisation and deoxygenation reactions, attention finally turned to the formal synthesis of Satavaptan 1 (Scheme 4). Coupling of the appropriately substituted aniline 4 with ketoacid 24 was carried out in the presence of propylphosphonic anhydride $(T3P)^{14}$ to give β -ketoamide 20, which, on treatment with stoichiometric Cu(OAc)2.H2O in refluxing mesitylene or ethylene carbonate delivered the requisite spirocyclic ketooxindole 19 in 58-62% yield. Ethylene carbonate has been shown to be an excellent green replacement for traditional organic solvents due to its low cost, ready availability, high flash point, low (eco)toxicity and excellent biodegradability.¹⁵ Pleasingly, in this instance, mesitylene was easily substituted for ethylene carbonate without a significant change in yield. Finally, deoxygenation was performed without incident via the 3-step sequence developed above to give Liotta's spirocyclic oxindole 12. This route therefore represents a new formal synthesis of Satavaptan, whilst removing the potentially dangerous diazo intermediates and costly rhodium salts used by Liotta et al.



Scheme 4. Formal total synthesis of Satavaptan.

In a final aspect to this work we wished to demonstrate the versatility of our route by applying it to the synthesis of a novel analogue of Satavaptan featuring a changed sulfonamide and a novel triazole side chain (**Scheme 5**). Mindful of the requirement to use the Birch reduction for cleavage of the benzyl protecting group used by Liotta, a different protecting group strategy was therefore adopted. In the event, the *para*-methoxybenzyl (PMB) group was chosen due to its potential removal under a wide variety of conditions (oxidation, acid, hydrogenolysis). In

 $(32\rightarrow 33)$, cross-dehydrogenative coupling using either EtO EtO T3F EtOAc, rt, 16 h MB NH PMB 32 24 33, 52% Cu(OAc)2•H2O (10 mol%) mesitylene, 165 °C, 20 min 1. HCI (aq), THF NaBH₄ 70 °C, 2 h EtO EtO EtC 2. H₂, Pd/C MeOH, 0 ℃, 1 h EtOAc, rt, 18 h PMB PMB PMB 34, 52% 36, 84% (2 steps) 35, 89% L-Selectride, THF –78 °C, 2 h NBn NaH OH N≈Ń BnN₃, Cul Br DIPEA EtO FtO THF THF. rt. o/n 50 °C, 20 h PMP PMB PMB 37,84% 38, 77% 39 TFA, reflux, 2 d NBn 'n≈'n NBn 'n≈Ń **FtO** KOt-Bu, ArSO₂CI THF, rt, 3 h Et(41.54% 40, 89% (2 steps)

Cu(OAc)₂·H₂O or Cu(2-ethylhexanoate)₂ as catalyst ($33\rightarrow 34$), and deoxygenation ($34\rightarrow 36$) proceeded without incident. *Syn*selective reduction of ketone **36** was accomplished under Liotta's conditions (L-Selectride, THF, -78 °C) to give alcohol **37**, which was subjected to alkylation with propargyl bromide. Huisgen cycloaddition of the subsequent alkyne **38** with benzyl azide in the presence of CuI delivered triazole **39**. Contrary to the benzyl deprotection above, removal of the PMB group was achieved on simple reflux with TFA to give N-H oxindole **40** (57% yield over 2 steps from **38**). Finally, deprotonation of **40** followed by addition of the aryl sulfonyl chloride delivered the novel Satavaptan analogue **41**.

3. Conclusions

The highly atom-economical radical cross-dehydrogenative coupling (CDC) of simple linear β -ketoamides **21** to give spirocyclic oxindoles **22** bearing 5-, 6- and 7-membered ring ketones has been established (Schemes 2 and 3). This approach was subsequently employed in the formal total synthesis of the vasopressin V₂ receptor antagonist Satavaptan (Scheme 4). CDC of linear anilide **20**, followed by deoxygenation in a three-step sequence involving reduction to the alcohol, dehydration, and hydrogenation delivered the key spirocyclic oxindole intermediate previously prepared by Liotta et al., and thus represents a new formal synthesis of Satavaptan. Finally, the

versatility of this approach was demonstrated by the synthesis of a novel Satavaptan analogue **41**.

4. Experimental section

4.1. General Methods

Except where stated, all reagents were purchased from commercial sources and used without further purification. ¹H and ³C NMR spectra were recorded on a JEOL ECX400 or ECS400 spectrometer, operating at 400 MHz and 100 MHz, respectively. All spectral data was acquired at 295 K. Chemical shifts (\delta) are quoted in parts per million (ppm). The residual solvent peak, $\delta_{\rm H}$ 7.27 and δ_C 77.0 for CDCl₃ was used as a reference. Coupling constants (J) are reported in Hertz (Hz). The multiplicity abbreviations used are: s singlet, d doublet, t triplet, q quartet, m multiplet. Signal assignment was achieved by analysis of DEPT, COSY, HMBC and HSQC experiments where required. Infrared (IR) spectra were recorded on a PerkinElmer UATR 2 spectrometer as a thin film dispersed from either CH₂Cl₂ or CDCl₃. Mass-spectra (low and high-resolution) were obtained by the University of York Mass Spectrometry Service, using electrospray ionisation (ESI) on a Bruker Daltonics, Micro-tof spectrometer. Melting points were determined using a Gallenkamp apparatus. Thin layer chromatography was carried out on Merck silica gel 60F254 pre-coated aluminium foil sheets and were visualised using UV light (254 nm) and stained with basic aqueous potassium permanganate. Flash column chromatography was carried out using slurry packed Fluka silica

Scheme 5. Synthesis of a novel Satavaptan analogue.

gel (SiO₂), 35–70 μ m, 60 Å, under a light positive pressure, M 37.5 (Me), 30.5 (CH₂), 26.9 (CH₂), 23.8 (CH₂); HRMS (ESI): eluting with the specified solvent system. MNa⁺, found 254.1149. C₁₄H₁₇NNaO₂ requires 254.1151.

4.2. Experimental procedures and compound characterisation

4.2.1. Synthesis of spirocyclic oxindoles 4.2.1.1. General procedure 1: Synthesis of linear anilides **21a-f**

The cyclic ketone (1 equiv) was added to a solution of magnesium methyl carbonate (2 M in DMF, 8 equiv). The reaction mixture was stirred at 130 °C for 6 h. After cooling to rt, 10% HCl solution was added until the pH became acidic. The aqueous phase was extracted with Et_2O , and the combined organic layers washed with H_2O and sat. brine, dried over MgSO₄, filtered, and concentrated in vacuo to give the carboxylic acid.

To a solution of the crude acid in CH_2Cl_2 (0.06 M) at 0 °C was added the aniline (1.15 equiv), 2-chloro-1-methylpyridinium iodide (1.4 equiv) and Et_3N (4.6 equiv). The reaction mixture was stirred at rt for 18 h, then quenched by the addition of 10% HCl. The layers were separated, and the aqueous phase extracted with CH_2Cl_2 . The combined organic layers washed with H_2O and sat. brine, dried over MgSO₄, filtered, and concentrated in vacuo to give the crude product. Purification by column chromatography on silica gel (Hexane/EtOAc, 3:1 to 1:4) gave the title compound.

4.2.1.2. N-Benzyl-2-oxo-N-phenylcyclopentane-1carboxamide (21a)

Following general procedure 1 from cyclopentanone (0.290 g, 2.26 mmol), methyl magnesium carbonate (2 M in DMF, 9.04 mL, 18.1 mmol) was obtained the carboxylic acid. Formation of the amide was carried out using N-benzylaniline (0.154 mL, 0.831 mmol), 2-chloro-1-methylpyridinium iodide (0.255 g, 0.997 mmol) and Et_3N (0.462 mL, 3.32 mmol) to give the title compound 21a (43 mg, 15%) as a colourless solid; mp. 97-99 ° C; v_{max} 2966, 1739, 1644, 1595, 1495, 1405, 700 cm⁻¹; δ_{H} (400 MHz; CDCl₃) 7.32-7.27 (3H, m), 7.27-7.23 (3H, m), 7.23-7.18 (2H, m), 7.13 (2H, br s), 5.01 (1H, d, J 14.4 Hz), 4.82 (1H, d, J 14.4 Hz), 3.08 (1H, dd, J 10.2, 9.2 Hz), 2.48-2.36 (1H, m), 2.35-2.24 (1H, m), 2.24-2.16 (1H, m), 2.14-2.03 (2H, m), 1.77-1.58 (1H, m); δ_{C} (100 MHz; CDCl₃) 214.8 (C), 170.1 (C), 142.1 (C), 137.1 (C), 129.6 (CH), 128.7 (2 × CH), 128.5 (CH), 128.3 (CH), 127.4 (CH), 53.3 (CH₂), 52.9 (CH), 38.6 (CH₂), 28.4 (CH₂), 21.1 (CH₂); HRMS (ESI): MNa^+ , found 316.1297. $C_{19}H_{19}NNaO_2$ requires 316.1308.

4.2.1.3. N-Methyl-2-oxo-N-phenylcyclohexane-1carboxamide (21b)

Following general procedure 1 from cyclohexanone (0.21 mL, 2.04 mmol), methyl magnesium carbonate (2 M in DMF, 8.15 mL, 16.3 mmol) was obtained the carboxylic acid. Formation of the amide was carried out using N-methylaniline (0.254 mL, 2.34 mmol), 2-chloro-1-methylpyridinium iodide (0.720 g, 2.82 mmol) and Et₃N (1.31 mL, 9.38 mmol) to give the title compound **21b** (65 mg, 30%) as a yellow oil; v_{max} 2941, 2865, 1710, 1652, 1595, 1495, 1450, 1421, 1382, 1126, 775, 702 cm⁻¹; $\delta_{\rm H}$ (400 MHz; CDCl₃) 7.37-7.35 (2H, m), 7.34-7.31 (1H, m), 7.15 (2H, dd, *J* 8.2, 1.3 Hz), 3.28 (3H, s), 3.21 (1H, dd, *J* 11.7, 5.9 Hz), 2.44-2.37 (1H, m), 2.16 (1H, ddd, *J* 15.4, 12.9, 3.6 Hz), 2.04-1.94 (2H, m), 1.94-1.83 (2H, m), 1.78-1.64 (1H, m), 1.51-1.37 (1H, m); $\delta_{\rm C}$ (100 MHz; CDCl₃) 207.5 (C), 169.7 (C), 143.8 (C), 129.9 (CH), 128.2 (CH), 127.3 (CH), 55.3 (CH), 41.7 (CH₂),

4.2.1.4. N-Methyl-2-oxo-Nphenylcycloheptanecarboxamide (**21c**)

A suspension of Pd/C (3 wt% on activated carbon, 84 mg) in EtOAc (10 mL) was thoroughly degassed three times while stirring. Benzyl 2-oxocycloheptanecarboxylate (0.247 g, 1.00 mmol) was added and the mixture stirred under an atmosphere of H_2 for 1 h. The suspension was filtered through Celite[®], washed with EtOAc, and concentrated in vacuo to give the crude acid as a colourless oil.

To a solution of the crude acid in CH₂Cl₂ (10 mL) at 0 °C was added N-methylaniline (0.062 mL, 0.570 mmol), 2chloromethylpyridinium iodide (0.210 g, 0.812 mmol) and Et₃N (0.400 mL, 2.64 mmol). The reaction was stirred at rt for 1 h, then quenched by the addition of 10% HCl (10 mL). The layers were separated, and the aqueous phase was extracted with EtOAc $(2 \times 10 \text{ mL})$. The combined organic extracts were washed with brine (2 \times 10 mL), dried over MgSO₄, filtered and concentrated in vacuo to give the crude product as a yellow oil. Purification by column chromatography on silica gel (Hexane/EtOAc, 6:1) gave the title compound **21c** (81 mg, 52%) as a colourless oil; v_{max} 2884, 1678, 1624, 1570, 1472, 1359, 1097 cm⁻¹; $\delta_{\rm H}$ (400 MHz; CDCl₃) 7.45-7.29 (3H, m), 7.22-7.16 (2H, m), 3.45 (1H, dd, J 10.6, 3.9 Hz), 3.25 (3H, s), 2.55 (1H, ddd, J 14.6, 11.6, 3.3 Hz), 2.14-2.04 (1H, m), 2.02-1.92 (1H, m), 1.92-1.81 (2H, m), 1.80-1.71 (2H, m), 1.40-1.03 (3H, m); δ_C (100 MHz; CDCl₃) 210.9 (C), 170.6 (C), 143.6 (C), 129.9 (CH), 128.2 (CH), 128.0 (CH), 56.6 (CH), 43.3 (CH₂), 37.6 (Me), 29.6 (CH₂), 28.6 (CH₂), 28.4 (CH₂), 24.60 (CH₂); HRMS (ESI): MH⁺, found 246.1497. C₁₅H₂₀NO₂ requires 246.1489.

4.2.1.5. N-(2,4-Dimethoxybenzyl)-2-oxo-N-phenylcycloheptanecarboxamide (21d)

A suspension of Pd/C (3 wt% on activated carbon, 0.403 g) in EtOAc (48 mL) was thoroughly degassed three times while stirring. Benzyl 2-oxocycloheptanecarboxylate (1.18 g, 4.80 mmol) was added and the mixture stirred under an atmosphere of H₂ for 1 h. The suspension was filtered through Celite[®], washed with EtOAc, and concentrated in vacuo to give the crude acid as a colourless oil.

To a solution of the crude acid in CH₂Cl₂ (48 mL) at 0 °C was added N-(2,4-dimethoxybenzyl)aniline (0.666 g, 2.74 mmol), 2chloromethylpyridinium iodide (0.980 g, 3.84 mmol) and Et₃N (1.76 mL, 12.6 mmol). The reaction was stirred at rt for 1 h, then quenched by the addition of 10% HCl (50 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (2 \times 50 mL). The combined organic extracts were washed with brine $(2 \times 50 \text{ mL})$, dried over MgSO₄, filtered and concentrated in vacuo to give the crude product as a yellow oil. Purification by column chromatography on silica gel (Hexane/EtOAc, 6:1) gave the title compound **21d** (0.470 g, 45%) as a colourless solid; mp. 66-68 °C; v_{max} 1705, 1650, 1614, 1594, 1508, 1495, 1454, 1262, 1209, 1157, 1037, 702 cm⁻¹; $\delta_{\rm H}$ (400 MHz; CDCl₃) 7.28-7.25 (3H, m), 7.26 (1H, d, J 8.3 Hz), 7.00 (2H, dd, J 7.6, 2.0 Hz), 6.42 (1H, dd, J 8.3, 2.4 Hz), 6.29 (1H, d, J 2.4 Hz), 4.90 (1H, d, J 14.5 Hz), 4.81 (1H, d, J 14.5 Hz), 3.76 (3H, s), 3.50 (3H, s), 3.44 (1H, dd, J 10.6, 3.9 Hz), 2.54 (1H, dd, J 8.8, 5.5 Hz), 2.10-1.95 (3H, m), 1.93-1.82 (2H, m), 1.75 (2H, dd, J 11.2, 4.6 Hz), 1.31-1.12 (2H, m); δ_C (100 MHz; CDCl₃) 211.0 (C), 170.4 (C), 160.2 (C), 158.5 (C), 142.1 (C), 131.0 (CH), 129.3 (CH), 129.1 (CH), 127.9 (CH), 117.9 (C), 104.2 (CH), 98.3 (CH), 56.9 (CH), 55.4 (Me), 55.1 (Me), 47.1 (CH₂), 43.4 (CH₂), 29.6 (CH₂), 28.7 (CH₂), 28.5

4.2.1.6. 5-(1-Hydroxypent-4-enylidene)-2,2dimethyl-1,3-dioxane-4,6-dione

A solution of DCC (4.74 g, 23.0 mmol) in CH₂Cl₂ (10 mL) was added slowly to a stirred solution of Meldrum's acid (3.01 g, 20.9 mmol), 4-pentenoic acid (2.13 mL, 20.9 mmol), and 4-(dimethylamino)pyridine (2.81 g, 23.0 mmol) in CH₂Cl₂ (30 mL) at 0 °C. The reaction mixture was allowed to warm to rt and stirred for 16 h. The suspension was filtered through Celite, and then washed with CH₂Cl₂ (50 mL). The filtrate was washed subsequently with 10% HCl (50 mL). The aqueous phase was extracted with CH_2Cl_2 (2 \times 20 mL). The combined organic phases were washed with water (2 \times 30 mL) and brine (2 \times 30 mL), dried over MgSO₄, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc) to give the title compound (3.32 g, 70%) as a yellow oil; v_{max} 1739, 1665, 1574, 1408, 1282, 1154, 1031, 919 cm⁻¹; δ_{H} (400 MHz; CDCl₃) 5.84 (1H, ddt, J 16.9, 10.2, 6.6 Hz), 5.08 (1H, dtd, J 16.9, 1.4, 1.3 Hz), 5.02 (1H, dtd, J 10.2, 1.4, 1.3 Hz), 3.19 (2H, dd, J 7.7, 6.6 Hz), 2.48 (1H, ddd, J 6.6, 6.6, 1.4 Hz), 2.45 (1H, ddd, J 7.7, 6.6, 1.4 Hz), 1.72 (6H, s); δ_C (100 MHz; CDCl₃) 197.2 (C), 170.6 (C), 160.3 (C), 136.1 (CH), 116.3 (CH₂), 105.0 (C), 91.7 (C), 35.1 (CH₂), 29.9 (CH₂), 26.9 (2 x Me); HRMS (ESI): MNa⁺, found 249.0742. C₁₁H₁₄NaO₅ requires 249.0733.

4.2.1.7. N-(4-Methoxybenzyl)-3-oxo-N-phenylhept-6-enamide

To a stirred solution of 5-(1-hydroxypent-4-enylidene)-2,2dimethyl-1,3-dioxane-4,6-dione (2.16 g, 9.55 mmol) in 1,4dioxane (14 mL) was added N-(4-methoxybenzyl)aniline (2.04 g, 9.55 mmol). The reaction mixture was stirred for 4 h at 110 °C, then the solvent was removed in vacuo and the residual oil was purified by column chromatography on silica gel (Hexane/EtOAc, 5:1) to give the title compound (2.81 g, 87%) as a yellow oil; v_{max} 1720, 1651, 1594, 1512, 1395, 1244, 1175, 1033, 821, 701 cm⁻¹; $\delta_{\rm H}$ (400 MHz; CDCl₃) 7.32-7.28 (3H, m), 7.12 (2H, d, J 8.7 Hz), 6.94 (2H, dd, J 6.5, 3.1 Hz), 6.78 (2H, d, J 8.7 Hz), 5.70 (1H, ddt, J 16.8, 10.2, 6.6 Hz), 4.94 (1H, dd, J 16.8, 1.5 Hz), 4.91 (1H, dd, J 10.2, 1.5 Hz), 4.83 (2H, s), 3.76 (3H, s), 3.27 (2H, s), 2.41 (2H, t, J 7.1 Hz), 2.21 (2H, td, J 7.1, 6.6 Hz); δ_C (100 MHz; CDCl₃) 203.7 (C), 166.7 (C), 159.0 (C), 141.9 (C), 136.8 (CH), 130.3 (CH), 129.7 (CH), 129.2 (C), 128.6 (CH), 128.5 (CH), 115.4 (CH₂), 113.8 (CH), 55.3 (Me), 52.5 (CH₂), 49.5 (CH₂), 42.3 (CH₂), 27.5 (CH₂); HRMS (ESI): MNa⁺ found 360.1561. C₂₁H₂₃NNaO₃ requires 360.1570.

4.2.1.8. N-(4-Methoxybenzyl)-2-(2-methylallyl)-3oxo-N-phenylhept-6-enamide

To a stirred solution of NaH (60% in mineral oil, 0.336 g, 8.41 mmol) in DMF (100 mL) was added N-(4-Methoxybenzyl)-3oxo-*N*-phenylhept-6-enamide (2.58 g, 7.65 mmol) at 0 °C. The reaction mixture was stirred for 15 min and allyl bromide (0.695 mL, 8.03 mmol) was added slowly. The resulting light green solution was stirred for 30 min and then allowed to warm to room temperature where it slowly turned yellow. The reaction mixture was stirred overnight and quenched with sat. NH₄Cl (100 mL). The aqueous layer was extracted with EtOAc (2 × 100 mL). The combined organic phases were washed with water (5 × 50 mL) and sat. brine (2 × 50 mL), dried over MgSO₄, filtered and concentrated in vacuo. Purification by column chromatography on silica gel (Petrol/EtOAc, 6:1) gave the title compound (3.21 g, quant.) as a light yellow oil; v_{max} 1717, 1650, 1613, 1594, 1512, 1394, 1302, 1245, 1176, 1033, 916, 702 cm⁻¹; $\delta_{\rm H}$ (400 MHz; CDCl₃) 7.34-7.29 (3H, m), 7.09 (2H, d, J 8.6 Hz), 6.90 (2H, dd, J 6.6, 3.1 Hz), 6.77 (2H, d, J 8.6 Hz), 5.75-5.58 (2H, m), 5.05-4.90 (4H, m), 4.82 (2H, s), 3.77 (3H, s), 3.35 (1H, dd, J 8.4, 5.9 Hz), 2.64 (1H, ddd, J 15.3, 8.4, 7.2 Hz), 2.47 (1H, ddd, J 15.3, 7.2, 5.9 Hz), 2.42-2.35 (1H, m), 2.29-2.21 (1H, m), 2.22-2.14 (2H, m); $\delta_{\rm C}$ (100 MHz; CDCl₃) 204.9 (C), 168.7 (C), 159.1 (C), 141.5 (C), 137.0 (CH), 135.1 (CH), 130.4 (CH), 129.8 (CH), 129.4 (C), 129.2 (CH), 128.5 (CH), 117.3 (CH₂), 115.3 (CH₂), 113.8 (CH), 56.9 (CH), 55.3 (Me), 52.8 (CH₂), 40.3 (CH₂), 33.6 (CH₂), 27.4 (CH₂); HRMS (ESI): MNa⁺, found 400.1878. C₂₄H₂₇NNaO₃ requires 400.1883.

4.2.1.9. Z-N-(4-Methoxybenzyl)-7-oxo-N-phenylcyclohept-3-enecarboxamide (21e)

To a degassed solution of N-(4-methoxybenzyl)-2-(2methylallyl)-3-oxo-N-phenylhept-6-enamide (0.493 g, 1.33 mmol) in CH₂Cl₂ (100 mL) was added Grubbs 2nd generation catalyst (52 mg, 0.067 mmol). The reaction mixture was stirred at 45 °C for 1 h. After cooling to rt, the solvent was removed in vacuo, and the residue was purified by column chromatography on silica gel (Petrol/EtOAc, 5:1 to 2:1) to give the title compound **21e** (0.264 g, 57%) as a colourless oil; v_{max} 1709, 1661, 1648, 1594, 1512, 1396, 1244, 1176, 1033, 702 cm⁻¹; $\delta_{\rm H}$ (400 MHz; CDCl₃) 7.30-7.26 (3H, m), 7.12 (2H, d, J 8.7 Hz), 6.94 (2H, dd, J 5.8, 3.8 Hz), 6.77 (2H, d, J 8.7 Hz), 5.68-5.56 (2H, m), 4.88 (1H, d, J 14.2 Hz), 4.77 (1H, d, J = 14.2 Hz), 3.80 (1H, dd, J 11.9, 3.9 Hz), 3.75 (3H, s), 2.79-2.71 (1H, m), 2.67 (1H, dd, J 14.9, 7.3 Hz), 2.43-2.34 (1H, m), 2.08-2.02 (2H, m), 2.01-1.93 (1H, m); δ_C (100 MHz; CDCl₃) 209.2 (C), 169.5 (C), 159.0 (C), 141.6 (C), 130.2 (CH), 129.6 (CH), 129.4 (C), 129.2 (CH), 129.1 (CH), 128.4 (CH), 128.2 (CH), 113.8 (CH), 55.3 (CH or Me), 55.2 (CH or Me), 52.5 (CH₂), 42.2 (CH₂), 28.4 (CH₂), 23.9 (CH₂); HRMS (ESI): MNa⁺, found 372.1573. C₂₂H₂₃NNaO₃ requires 372.1570.

4.2.1.10. N-(4-Methoxybenzyl)-4-oxo-N-phenyl-8oxabicyclo[5.1.0]octane-3-carboxamide (**21f**)

To a stirred solution of (Z)-N-(4-methoxybenzyl)-7-oxo-Nphenylcyclohept-3-enecarboxamide 21e (0.122 g, 0.348 mmol) in acetone (2 mL) at 0 °C was added a solution of DMDO (0.06 M in acetone, 11.1 mL, 0.696 mmol). The reaction mixture was stirred at 0 °C for 1 h and allowed to warm to rt for a further 1 h. The solvent was removed in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/Petrol 2:1) to give the title compound 21f (0.108 g, 85%) as a colourless oil and inseparable 1:1.5 mixture of diastereoisomers; v_{max} 1710, 1657, 1594, 1594, 1512, 1396, 1244, 1176, 1031, 730, 702 $\mbox{cm}^{-1};\ \delta_{H}$ (400 MHz; CDCl₃) 7.31-7.26 (3H, m), 7.14-7.06 (2H, m), 6.92-6.84 (2H, m), 6.80-6.74 (2H, m), 4.84 (1H, d, J 14.3 Hz), 4.77 (0.4H, d, J 14.3 Hz), 4.75 (0.6H, d, J 14.3 Hz), 3.75 (3H, s), 3.66-3.58 (1H, m), 3.17 (1H, td, J 4.6, 1.7 Hz), 3.06-3.01 (1H, m), 2.54- 2.34 (2H, m), 2.09 (0.6H, ddd, J 12.1, 7.5, 4.4 Hz), 2.01-1.93 (2H, m), 1.82 (1.4H, ddd, J 12.1, 9.8, 4.4 Hz); δ_C (100 MHz; CDCl₃) 209.3 and 207.4 (C), 168.9 and 168.7 (C), 159.0 (C), 141.3 and 141.2 (C), 130.2 and 130.1 (CH), 129.74 and 129.70 (CH), 129.4 (CH), 129.31 and 129.26 (C), 128.5 (CH), 113.8 (CH), 55.3 (Me), 54.4 (CH), 54.0 and 53.3 (CH), 52.6 and 52.5 (CH₂), 51.7 and 51.4 (CH), 38.0 and 36.3 (CH₂), 28.6 and 27.3 (CH₂), 24.0 and 22.7 (CH₂); HRMS (ESI): MNa⁺, found 388.1504. C₂₂H₂₃NNaO₄ requires 388.1519.

4.2.1.11. General procedure 2: Copper(II)-mediated synthesis of spirocyclic oxindoles **22a-f**

To a stirred solution of linear amide **21** (1 equiv) in toluene (0.04 M) was added $Cu(OAc)_2 \cdot H_2O$ (10 mol%-1 equiv) under an O_2 atmosphere. The reaction mixture was heated at 110 °C for

1.5 h then cooled to room temperature and the solvent was M removed in vacuo. The residue was filtered through Celite[®], washed with CH_2Cl_2 and concentrated in vacuo to give the crude product. Purification by column chromatography on silica gel (Hexane/EtOAc, 4:1) gave the title compound.

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4.2.1.12. 1'-Benzyl-1',2'-
dihydrospiro[cyclopentane-1,3'-indole]-2',5-dione
(22a)
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Following general procedure 2 from *N*-benzyl-2-oxo-*N*-phenylcyclopentane-1-carboxamide **21a** (11.0 mg, 0.037 mmol) was obtained the title compound **22a** (6.0 mg, 56%) as a colourless oil; v_{max} 2969, 1747, 1702, 1611, 1489, 1466, 1360, 1183, 1107, 754, 697 cm⁻¹; $\delta_{\rm H}$ (400 MHz; CDCl₃) 7.34–7.24 (5H, m), 7.16 (1H, td, *J* 7.7, 1.3 Hz), 7.09 (1H, dd, *J* 7.2, 1.2 Hz), 7.00 (1H, td, *J* 7.6, 1.0 Hz), 6.69 (1H, d, *J* 7.9 Hz), 5.00 (1H, d, *J* 15.8 Hz), 4.80 (1H, d, *J* 15.8 Hz), 2.79–2.70 (1H, m), 2.70–2.61 (1H, m), 2.60–2.48 (2H, m), 2.46–2.37 (1H, m), 2.32–2.19 (1H, m); $\delta_{\rm C}$ (100 MHz; CDCl₃) 212.7 (C), 175.4 (C), 143.5 (C), 135.4 (C), 130.5 (C), 128.9 (CH), 128.7 (CH), 127.7 (CH), 127.1 (CH), 123.0 (CH), 122.6 (CH), 109.6 (CH), 63.1 (C), 43.9 (CH₂), 38.4 (CH₂), 34.2 (CH₂), 20.4 (CH₂); HRMS (ESI): MNa⁺, found 314.1154. C₁₉H₁₇NNaO₂ requires 314.1151.

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4.2.1.13. 1'-Methyl-1'-2'-
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dihydrospiro[cyclohexane-1,3'-indole]-2',6-dione
(22b)

Following general procedure 2 from *N*-methyl-2-oxo-*N*-phenylcyclohexane-1-carboxamide **21b** (0.016 g, 0.067 mmol) was obtained the title compound **22b** (0.010 g, 65%) as a colourless oil; v_{max} 2940, 2867, 1730, 1697, 1613, 1494, 1471, 1373, 1348, 1127, 754 cm⁻¹; δ_{H} (400 MHz; CDCl₃) 7.30 (1H, td, *J* 7.6, 1.1 Hz), 7.28 (1H, d, *J* 7.3 Hz), 7.09 (1H, td, *J* 7.5, 0.9 Hz), 6.83 (1H, d, *J* 7.8 Hz), 3.19 (3H, s), 3.05 (1H, ddd, *J* 14.2, 10.5, 5.5 Hz), 2.58 (1H, dt, *J* 14.2, 5.5 Hz), 2.41 (1H, dtt, *J* 14.2, 10.5, 4.0 Hz), 2.27–2.13 (2H, m), 2.08 (1H, ddd, *J* 14.2, 10.5, 4.0 Hz), 2.03–1.92 (1H, m), 1.90–1.81 (1H, m); δ_{C} (100 MHz; CDCl₃) 205.4 (C), 174.4 (C), 143.3 (C), 129.5 (C), 128.8 (CH), 124.7 (CH), 122.8 (CH), 108.5 (CH), 63.8 (C), 39.9 (CH₂), 37.4 (CH₂), 27.0 (CH₂), 26.6 (CH₃), 20.4 (CH₂); HRMS (ESI): MNa⁺, found 252.0998. C₁₄H₁₅NNaO₂ requires 252.0995.

4.2.1.14. 1'-Methylspiro[cycloheptane-1,3'indoline]-2,2'-dione (**22c**)

Following general procedure 2 from *N*-methyl-2-oxo-*N*-phenylcycloheptanecarboxamide **21c** (0.037 g, 0.152 mmol) was obtained the title compound **22c** (0.024 g, 66%) as a colourless oil; v_{max} 2889, 1703, 1668, 1585, 1471, 1447, 1352, 1325 cm⁻¹; δ_{H} (400 MHz; CDCl₃) 7.29 (1H, td, *J* 7.7, 1.2 Hz), 7.25 (1H, ddd, *J* 7.7, 1.2, 0.5 Hz), 7.06 (1H, td, *J* 7.7, 1.2 Hz), 6.83 (1H, d, *J* 7.7 Hz), 3.19 (3H, s), 3.09–3.01 (1H, m), 2.78–2.67 (1H, m), 2.31 (1H, dd, *J* 14.8, 9.1 Hz), 2.17–2.09 (1H, m), 2.07–1.95 (1H, m), 1.94–1.84 (1H, m), 1.84–1.73 (4H, m); δ_{C} (100 MHz; CDCl₃) 207.6 (C), 175.3 (C), 143.5 (C), 130.8 (C), 128.7 (CH), 123.6 (CH), 122.7 (CH), 108.6 (CH), 65.6 (C), 42.3 (CH₂), 34.8 (CH₂), 30.9 (CH₂), 26.8 (CH₂), 26.5 (Me), 25.4 (CH₂); HRMS (ESI): MH⁺, found 244.1334. C₁₅H₁₈NO₂ requires 244.1332.

4.2.1.15. 1'-(2,4-

Dimethoxybenzyl)spiro[cycloheptane-1,3'-indoline]-2,2'-dione (22d)

Following general procedure 2 from N-(2,4dimethoxybenzyl)-2-oxo-N-phenylcycloheptanecarboxamide **21d** (0.306 g, 0.798 mmol) was obtained the title compound **22d** (0.206 g, 68%) as a colourless solid; R_f 0.40 (Hexane/EtOAc, 3:1); v_{max} 1716, 1692, 1609, 1590, 1508, 1465, 1361, 1208, 1156, 1035, 746 cm⁻¹; $\delta_{\rm H}$ (400 MHz; CDCl₃) 7.24 (1H, dd, *J* 7.5, 1.0 Hz), 7.17 (1H, td, *J* 7.5, 1.0 Hz), 7.06 (1H, d, *J* 8.4 Hz), 7.01 (1H, td, *J* 7.5, 1.0 Hz), 6.77 (1H, d, *J* 7.5 Hz), 6.44 (1H, d, *J* 2.4 Hz), 6.38 (1H, dd, *J* 8.4, 2.4 Hz), 4.89 (1H, d, *J* 16.0 Hz), 4.80 (1H, d, *J* 16.0 Hz), 3.84 (3H, s), 3.75 (3H, s), 3.05 (1H, td, *J* 9.0, 2.1 Hz), 2.76 (1H, td, *J* 9.0, 2.1 Hz), 2.37 (1H, dd, *J* 14.7, 8.8 Hz), 2.22–2.12 (1H, m), 2.05 (1H, dd, *J* 14.7, 9.4 Hz), 1.97–1.73 (5H, m); $\delta_{\rm C}$ (100 MHz; CDCl₃) 207.7 (C), 175.7 (C), 160.4 (C), 158.1 (C), 143.0 (C), 130.7 (C), 129.1 (CH), 128.6 (CH), 123.4 (CH), 122.5 (CH), 116.0 (C), 109.8 (CH), 104.4 (CH), 98.5 (CH), 65.6 (C), 55.5 (Me), 55.4 (Me), 42.5 (CH₂), 38.2 (CH₂), 34.9 (CH₂), 31.0 (CH₂), 26.7 (CH₂), 25.4 (CH₂); HRMS (ESI): MNa⁺, found 402.1665. C₂₃H₂₅NNaO₄ requires 402.1676.

4.2.1.16. (Z)-1'-(4-Methoxybenzyl)spiro[cyclohept[3]ene-1,3'indoline]-2',7-dione (22e)

Following general procedure 2 from (Z)-N-(4methoxybenzyl)-7-oxo-N-phenylcyclohept-3-enecarboxamide 21e (0.024 g, 0.068 mmol) at 100 °C was obtained the title compound 22e (0.013 g, 55%) as a colourless solid; mp. 125-127 °C; v_{max} 1697, 1610, 1514, 1487, 1466, 1352, 1248, 1178, 1033, 750 cm⁻¹; $\delta_{\rm H}$ (400 MHz; CDCl₃) 7.28 (1H, dd, J 7.6, 1.0 Hz), 7.20 (2H, d, J 8.7 Hz), 7.17 (1H, td, J 7.6, 1.0 Hz), 6.99 (1H, td, J 7.6, 1.0 Hz), 6.83 (2H, d, J 8.7 Hz), 6.72 (1H, d, J 7.6 Hz), 5.95-5.80 (2H, m), 4.88 (1H, d, J 15.5 Hz), 4.77 (1H, d, J 15.5 Hz), 3.76 (3H, s), 3.60 (1H, dd, J 14.2, 8.1 Hz), 3.41 (1H, ddd, J 15.4, 4.7, 2.2 Hz), 2.76-2.65 (2H, m), 2.63-2.50 (1H, m), 2.35 (1H, dd, J 15.4, 7.4 Hz); δ_C (100 MHz; CDCl₃) 206.6 (C), 174.2 (C), 159.1 (C), 142.9 (C), 131.0 (CH), 130.6 (C), 128.8 (CH), 128.5 (CH), 127.5 (C), 125.6 (CH), 124.2 (CH), 122.8 (CH), 114.3 (CH), 109.6 (CH), 67.8 (C), 55.3 (Me), 43.4 (CH₂), 39.0 (CH₂), 31.4 (CH₂), 27.7 (CH₂); HRMS (ESI): MNa⁺ found 370.1410. C₂₂H₂₁NNaO₃ requires 370.1414.

4.2.1.17. 1'-(4-Methoxybenzyl)-8oxaspiro[bicyclo[5.1.0]octane-3,3'-indoline]-2',4dione (22f)

Following general procedure 2 from N-(4-methoxybenzyl)-4oxo-N-phenyl-8-oxabicyclo[5.1.0]octane-3-carboxamide (0.027 g, 0.073 mmol) was obtained the title compound 22f (0.015 g, 62%) as a pale yellow oil; v_{max} 1698, 1611, 1514, 1488, 1466, 1362, 1248, 1178, 1033, 751 cm⁻¹; $\delta_{\rm H}$ (400 MHz; CDCl₃) 7.55 (1H, dd, J 7.6, 1.0 Hz), 7.20 (1H, td, J 7.6, 1.0 Hz), 7.17 (2H, d, J 8.8 Hz), 7.08 (1H, td, J 7.6, 1.0 Hz), 6.83 (2H, d, J 8.8 Hz), 6.73 (1H, d, J 7.6 Hz), 4.87 (1H, d, J 15.6 Hz), 4.76 (1H, d, J 15.6 Hz), 3.75 (3H, s), 3.43 (1H, ddd, J 6.9, 3.9, 2.4 Hz), 3.31 (1H, dt, J 3.9, 2.8 Hz), 3.19 (1H, dd, J 8.4, 3.0 Hz), 3.13 (1H, dd, J 15.7, 2.4 Hz), 2.54–2.47 (3H, m), 2.41 (1H, dd, J 15.7, 6.9 Hz); δ_C (100 MHz; CDCl₃) 204.0 (C), 173.9 (C), 159.2 (C), 142.9 (C), 130.3 (C), 128.8 (CH), 128.5 (CH), 127.4 (C), 125.6 (CH), 123.4 (CH), 114.3 (CH), 109.5 (CH), 63.8 (C), 55.3 (Me), 55.2 (CH), 54.3 (CH), 43.5 (CH₂), 35.8 (CH₂), 32.8 (CH₂), 25.9 (CH₂); HRMS (ESI): MNa^+ found 386.1369. $C_{22}H_{21}NNaO_4$ requires 386.1363.

4.2.2. Synthesis of a Satavaptan model system 4.2.2.1. N-Methyl-N-phenyl 7-oxo-1,4dioxaspiro[4.5]decane-8-carboxamide (25)

A solution of benzyl 7-oxo-1,4-dioxaspiro[4.5]decane-8carboxylate (2.07 g, 7.13 mmol) and 10% Pd/C (0.414 g) in EtOAc (71 mL) was evacuated and backfilled with H₂ four times. The reaction mixture was stirred under an atmosphere of H₂ (balloon) for 16 h, then filtered through a pad of Celite which

To a solution of 7-oxo-1,4-dioxaspiro[4.5]decane-8carboxylic acid 24 (1.40 g, 6.99 mmol) in CH₂Cl₂ (71 mL) at 0 °C was added N-methylaniline (0.93 mL, 8.56 mmol), 2-chloro-1-methylpyridinium iodide (2.73 g, 10.7 mmol) and Et₃N (2.98 mL, 21.4 mmol). The reaction mixture was stirred at 0 °C for 30 min, then at rt for 19 h. H₂O (150 mL) was then added, the organics separated, and the aqueous phase further extracted with CH_2Cl_2 (2 × 150 mL). The combined organics were washed with saturated NaHCO₃ (150 mL), dried over MgSO₄, filtered, and concentrated in vacuo. Purification by flash column chromatography, eluting with EtOAc/Hexane (1:1), afforded the title compound 25 (1.24 g, 60%) as a pale yellow solid; mp 105-107 °C; v_{max} 2918, 1715, 1656, 1595, 1489, 1421, 1385, 1307, 1237, 1131, 1091, 1032 cm $^{\text{-1}};\,\delta_{\text{H}}$ (400 MHz; CDCl₃) 7.40-7.31 (3H, m), 7.18-7.16 (2H, m), 3.95-3.86 (4H, m), 3.29 (3H, s), 3.21 (1H, dd, J 10.2, 6.0 Hz), 2.70 (1H, dd, J 14.1, 2.1 Hz), 2.32 (1H, d, J 14.1 Hz), 2.27-2.17 (1H, m), 2.09-2.03 (1H, m), 1.92-1.84 (1H, m), 1.74-1.67 (1H, m).; δ_C (100 MHz; CDCl₃) 203.0 (C), 168.8 (C), 143.4 (C), 129.7 (CH), 128.1 (CH), 127.1 (CH), 109.4 (C), 64.55 (CH₂), 64.51 (CH₂), 53.2 (CH), 51.0 (CH₂), 37.3 (Me), 32.7 (CH₂), 23.9 (CH₂).; HRMS (ESI): MNa⁺, found 312.1196. C₁₆H₁₉NNaO₄ requires 312.1206.

4.2.2.2. 1''-Methyl-1'',2''-dihydrodispiro[1,3dioxolane-2,1'-cyclohexane-4',3''-indole]-2'',3'dione (**26**)

А solution of *N*-methyl-*N*-phenyl 7-oxo-1,4dioxaspiro[4.5]decane-8-carboxamide 25 (0.430 g, 1.49 mmol) and Cu(OAc)₂·H₂O (30.0 mg, 0.150 mmol) in mesitylene (30 mL) was heated at reflux for 15 min whilst compressed air (dried over H₂SO₄) was bubbled through the mixture. After cooling to rt, the reaction mixture was concentrated in vacuo. Purification by flash column chromatography, eluting with EtOAc/Hexane (1:9 to 1:4), afforded the title compound (0.222 g, 52%) as a colourless solid; mp 124–125 °C; v_{max} 2969, 1723, 1694, 1656, 1606, 1489, 1348, 1309, 1236, 1122, 1089, 1066 cm⁻¹; $\delta_{\rm H}$ (400 MHz; CDCl₃) 7.32 (1H, td, J 7.7, 1.3 Hz), 7.24 (1H, dd, J 7.4, 0.7 Hz), 7.13 (1H, td, J 7.6, 0.9 Hz), 6.85 (1H, d, J 7.7 Hz), 4.06-4.00 (4H, m), 3.50 (1H, d, J 13.5 Hz), 3.20 (3H, s), 2.81 (1H, td, J 12.9, 4.9 Hz), 2.77 (1H, dd, J 13.5, 2.4 Hz), 2.26 (1H, td, J 12.5, 4.4 Hz), 2.10 (1H, dt, J 14.0, 4.1 Hz), 1.97-1.93 (1H, m); $\delta_{\rm C}$ (100 MHz; CDCl₃) 200.9 (C), 173.4 (C), 143.3 (C), 128.9 (CH), 128.8 (C), 125.1 (CH), 123.1 (CH), 110.0 (C), 108.5 (CH), 65.1 (CH₂), 64.8 (CH₂), 62.4 (C), 49.8 (CH₂), 31.6 (CH₂), 30.4 (CH₂), 26.6 (Me).; HRMS (ESI): MNa⁺, found 310.1040. C₁₆H₁₇NNaO₄ requires 310.1050.

4.2.2.3. 3'-Hydroxy-1''-methyl-1'',2''dihydrodispiro[1,3-dioxolane-2,1'-cyclohexane-4',3''-indole]-2''-one (27)

To a solution of 1''-methyl-1'',2''-dihydrodispiro[1,3dioxolane-2,1'-cyclohexane-4',3''-indole]-2'',3'-dione **26** (0.197 g, 0.686 mmol) in MeOH (6.9 mL) at 0 °C was added NaBH₄ (39.0 mg, 1.03 mmol). Stirring was continued at 0 °C for 1 h, then saturated NH₄Cl (20 mL) was added and the aqueous phase extracted with EtOAc (3×20 mL). The combined organics were dried over MgSO₄, filtered, and concentrated *in vacuo*. Purification by flash column chromatography, eluting with EtOAc/Hexane (1:1), afforded the title compound (0.185 g, 93%) as a colourless solid; mp 169–171 °C; v_{max} 3394, 2896, 1673, 4609, 1491, 1470, 1417, 1377, 1358, 1238, 1126, 1095, 1070, 1039 cm⁻¹; $\delta_{\rm H}$ (400 MHz; CDCl₃) 7.51 (1H, dd, *J* 7.5, 0.4 Hz), 7.31 (1H, td, *J* 7.8, 1.1 Hz), 7.06 (1H, td, *J* 7.6, 0.9 Hz), 6.86 (1H, d, *J* 7.7 Hz), 4.10-3.98 (5H, m), 3.21 (3H, s), 2.50-2.46 (1H, m), 2.20-2.17 (1H, m), 2.05-1.84 (4H, m); $\delta_{\rm C}$ (100 MHz; CDCl₃) 178.3 (C), 143.7 (C), 130.4 (C), 128.2 (CH), 125.6 (CH), 122.2 (CH), 108.8 (C), 107.9 (CH), 71.0 (CH), 64.5 (CH₂), 64.4 (CH₂), 52.7 (C), 37.9 (CH₂), 30.0 (CH₂), 28.1 (CH₂), 26.3 (Me); HRMS (ESI): MNa⁺, found 312.1212. C₁₆H₁₉NNaO₄ requires 312.1206.

4.2.2.4. 1'-Methyl-1',2'-dihydrospiro[cyclohexane-1,3'-indol]-2-ene-2',4-dione (**29**)

То of 3'-hydroxy-1"-methyl-1",2"а solution dihydrodispiro[1,3-dioxolane-2,1'-cyclohexane-4',3''-indole]-2"-one 27 (29.0 mg, 0.100 mmol) in THF (0.5 mL) was added 10% aqueous HCl (0.2 mL). The reaction mixture was heated at reflux for 1 h, then cooled to rt and partitioned between saturated NaHCO₃ (10 mL) and EtOAc (3 \times 10 mL). The combined organics were dried over MgSO₄, filtered, and concentrated in vacuo. Purification by flash column chromatography, eluting with EtOAc/Hexane (1:9 to 1:1), afforded the title compound as a colourless oil (16.9 mg, 74%); v_{max} 3056, 2934, 1704, 1674, 1607, 1491, 1469, 1418, 1383, 1370, 1344, 1301, 1267, 1255, 1237, 1189, 1126, 1089 cm⁻¹; $\delta_{\rm H}$ (400 MHz; CDCl₃) 7.35 (1H, td, J 7.7, 1.2 Hz), 7.19 (1H, dd, J 7.4, 0.7 Hz), 7.09 (1H, td, J 7.6, 0.7 Hz), 6.90 (1H, d, J 7.7 Hz), 6.46 (1H, d, J 10.1 Hz), 6.24 (1H, d, J 10.1 Hz), 3.25 (3H, s), 3.11 (1H, ddd, J 17.2, 9.8, 5.3 Hz), 2.60 (1H, ddd, J 17.2, 9.8, 5.3 Hz), 2.43-2.36 (1H, m), 2.27 (1H, ddd, J 14.0, 9.8, 5.1 Hz); δ_C (100 MHz; CDCl₃) 198.1 (C), 176.3 (C), 146.2 (CH), 143.1 (C), 131.5 (CH), 131.2 (C), 129.2 (CH), 123.7 (CH), 123.1 (CH), 108.7 (CH), 49.7 (C), 33.2 (CH₂), 32.0 (CH₂), 26.6 (Me); HRMS (ESI): MNa⁺, found 250.0843. C₁₄H₁₃NNaO₂ requires 250.0838.

4.2.2.5. 1'-Methyl-1',2'-dihydrospiro[cyclohexane-1,3'-indole]-2',4-dione (**30**)

A solution of 1'-methyl-1',2'-dihydrospiro[cyclohexane-1,3'indol]-2-ene-2',4-dione 29 (16.9 mg, 0.074 mmol) and 10% Pd/C (3.4 mg) in EtOAc (1 mL) was evacuated and backfilled with H₂ 4 times. The reaction mixture was stirred under an atmosphere of H₂ (balloon) for 16 h, then filtered through a pad of Celite which was washed with EtOAc (3 \times 15 mL). The combined organics were concentrated in vacuo to afford the title compound as a colourless solid (16.0 mg, 94%); mp 128–130 °C; v_{max} 2927, 1700, 1609, 1493, 1467, 1443, 1377, 1347, 1330, 1301, 1228, 1186, 1131, 1085 cm⁻¹; $\delta_{\rm H}$ (400 MHz; CDCl₃) 7.32 (1H, td, J 7.7, 1.0 Hz), 7.24 (1H, d, J 7.3 Hz), 7.09 (1H, td, J 7.6, 0.6 Hz), 6.89 (1H, d, J 7.8 Hz), 3.25 (3H, s), 3.17 (2H, ddd, J 16.1, 8.8, 8.8 Hz), 2.48 (2H, ddd, J 15.0, 5.4, 5.4 Hz), 2.15 (4H, dd, J 8.8, 5.4 Hz); δ_{C} (100 MHz; CDCl₃) 210.9 (C), 179.3 (C), 142.9 (C), 133.3 (C), 128.4 (CH), 122.8 (CH), 122.6 (CH), 108.5 (CH), 45.6 (C), 37.0 (CH₂), 33.7 (CH₂), 26.3 (Me).; HRMS (ESI): MNa⁺, found 252.0983. C₁₄H₁₅NNaO₂ requires 252.0995.

4.2.3. Formal total synthesis of Satavaptan 4.2.3.1. N-Benzyl-N-(4-ethoxyphenyl)-7-oxo-1,4dioxaspiro[4.5]decane-8-carboxamide (**20**)

To a stirred solution of ethyl 7-oxo-1,4dioxaspiro[4.5]decane-8-carboxylate **24** (0.577 g, 1.41 mmol), *N*benzyl-4-ethoxyaniline **4** (0.141 g, 0.705 mmol) and DIPEA (311 μ L, 1.83 mmol) in EtOAc (9 mL) at room temperature was added T3P (0.897 g, 1.41 mmol, 50% w/w solution in EtOAc). The reaction mixture was stirred at room temperature for 16 h. Saturated NaHCO₃ (10 mL) was added and the aqueous phase extracted with EtOAc (10 × 5 mL). The combined organic

extracts were washed with saturated NaHCO₃ (10 mL), brine \mathbb{N} (10 mL), dried over MgSO₄, filtered and concentrated in vacuo. Purification by flash column chromatography (1:1)hexane/EtOAc) afforded the title compound 20 (0.220 g, 76%) as a colourless oil; v_{max} 2978, 1718, 1657, 1511, 1401, 1301, 1247 cm⁻¹; $\delta_{\rm H}$ (400 MHz; CDCl₃): 7.28-7.16 (5H, m), 6.83 (2H, d, J 8.9 Hz), 6.73 (2H, d, J 8.9 Hz), 5.00 (1H, d, J 14.4 Hz), 4.73 (1H, d, J 14.4 Hz), 3.98-3.85 (6H, m), 3.21 (1H, dd, J 5.95, 4.12 Hz), 2.66 (1H, d, J 14.0 Hz), 2.31 (1H, d, J 14.0 Hz), 2.34-2.20 (1H, m), 2.07-2.20 (1H, m), 1.96-1.87 (1H, m), 1.72 (1H, td, J 12.8, 4.12 Hz), 1.37 (3H, t, J 6.9 Hz); δ_C (100 MHz, CDCl₃): 203.3 (C), 169.4 (C), 158.7 (C), 137.4 (C), 134.3 (C), 129.5 (CH), 128.9 (CH), 128.4 (CH), 127.4 (CH), 115.1 (CH), 109.7 (C), 64.9 (CH₂), 63.7 (CH₂), 53.7 (CH), 53.3 (CH₂), 51.4 (CH₂), 33.1 (CH₂), 24.1 (CH₂), 14.8 (Me); HRMS [ESI]: MNa^+ , found 432.1776. C₂₄H₂₇NNaO₅ requires 432.1781.

4.2.3.2. 1''-Benzyl-5''-ethoxy-2'H-dispiro[1,3dioxolane-2,4'-cyclohexane-1',3''-indole]-2',2''(1''H)-dione (19)

In mesitylene: N-Benzyl-N-(4-ethoxyphenyl)-7-oxo-1,4dioxaspiro[4.5]decane-8-carboxamide **20** (80.0 mg, 0.196 mmol) and Cu(OAc)₂·H₂O (3.9 mg, 10 mol%) in mesitylene (4 mL) was stirred at 165 °C with compressed air bubbled through for 30 min. Upon completion of the reaction, mesitylene was removed under reduced pressure and EtOAc (5 mL) was added. The organic phase was washed with 10% HCl solution (2 × 5 mL), 10% NH₄OH solution (2 × 5 mL), brine (5 ml), dried over MgSO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (7:3 petrol/EtOAc) afforded the title compound **19** (46.0 mg, 58%) as a yellow oil.

In ethylene carbonate: N-Benzyl-N-(4-ethoxyphenyl)-7-oxo-1,4-dioxaspiro[4.5]decane-8-carboxamide 20 (55.0 mg, 0.134 mmol) and Cu(OAc)₂·H₂O (26.8 mg, 0.134 mmol) in ethylene carbonate (3.3 mL) was stirred at 165 °C under an atmosphere of air for 1 h. The reaction mixture was removed from heat and allowed to cool to rt, then H₂O (8 mL) and EtOAc (8 mL) were added and the reaction mixture allowed to cool to room temperature. The reaction mixture was transferred to a separating funnel to which EtOAc (15 mL) was added and the organic phase washed with H₂O (5 \times 10 mL), 10% aqueous NH₄OH solution (3 \times 5 mL), brine (5 mL), dried (MgSO₄), filtered and concentrated in vacuo. Purification by flash column chromatography (7:3 hexane/EtOAc) afforded the title compound **19** (34.0 mg, 62%) as a yellow oil; v_{max} 2978, 1718, 1698, 1496, 1455, 1352, 1300 cm⁻¹; δ_H (400 MHz, CDCl₃): 7.25-7.12 (5H, m), 6.77 (1H, d, J 2.3 Hz), 6.63 (1H, dd, J 8.4, 2.3 Hz), 6.51 (1H, d, J 8.4 Hz), 4.79 (2H, s), 4.01-3.83 (6H, m), 3.46 (1H, d, J 13.7 Hz), 2.77 (1H, td, J 12.9, 4.9 Hz), 2.72 (1H, d, J 13.7 Hz), 2.29-2.16 (1H, m), 2.09 (1H, dt, *J* 14.1, 4.6 Hz), 1.93-1.86 (1H, m), 1.30 (3H, t, *J* 6.9 Hz); δ_C (100 MHz, CDCl₃): 200.8 (C), 173.2 (C), 155.5 (C), 135.54 (C), 135.47 (C), 129.9 (C), 128.8 (CH), 127.6 (CH), 127.0 (CH), 114.1 (CH), 113.9 (CH), 112.6 (CH), 109.8 (C), 65.0 (CH₂), 64.7 (CH₂), 64.0 (CH₂), 62.6 (C), 49.8 (CH₂), 43.9 (CH₂), 31.8 (CH₂), 30.4 (CH₂), 14.8 (Me); HRMS [ESI]: MNa⁺, found 430.1620. C₂₄H₂₅NNaO₅ requires 430.1625.

4.2.3.3. 1''-Benzyl-5''-ethoxy-3'hydroxydispiro[1,3-dioxolane-2,1'-cyclohexane-4',3''-indol]-2''(1''H)-one (**31**)

To a stirred solution of 1"-benzyl-5"-ethoxy-2'H-dispiro[1,3-dioxolane-2,4'-cyclohexane-1',3"-indole]-2',2"(1"H)-dione **19** (0.355 g, 0.872 mmol) in MeOH (10.5 mL) at 0 °C was added NaBH₄ (49.5 mg, 1.31 mmol) and stirred for 2 h. The reaction mixture was quenched with NH₄Cl (10 mL) then the aqueous

phase was extracted with EtOAc (2×10 mL). The combined organic phases were dried (MgSO₄), filtered and concentrated in vacuo. Purification by flash column chromatography (1:1 hexane/EtOAc) afforded a single diastereoisomer of the title compound 31 (0.284 g, 80%) as a colourless powder; m.p. 174-175 °C; v_{max} 3452, 2933, 1698, 1597, 1496, 1455, 1442, 1351 cm⁻ ¹; $\delta_{\rm H}$ (400 MHz, CDCl₃): 7.31-7.19 (5H, m), 7.16 (1H, d, J 2.5 Hz), 6.68 (1H, dd, J 8.5, 2.5 Hz), 6.57 (1H, d, J 8.5 Hz), 4.98 (1H, d, J 16.0 Hz), 4.81 (1H, d, J 16.0 Hz), 4.20-3.91 (7H, m), 2.60-2.46 (1H, m), 2.25-2.13 (1H, m), 2.09-1.96 (3H, m), 1.94-1.86 (1H, m), 1.37 (3H, t, J 7.0 Hz); δ_C (100 MHz, CDCl₃): 178.3 (C), 154.9 (C), 136.3 (C), 136.0 (C), 128.8 (CH), 127.5 (CH), 127.1 (C), 127.0 (CH), 114.5 (CH), 112.7 (CH), 109.3 (CH), 108.9 (C), 73.4 (CH), 71.3 (C), 64.6 (CH₂), 64.5 (CH₂), 64.1 (CH₂), 43.7 (CH₂), 38.1 (CH₂), 30.1 (CH₂), 28.4 (CH₂), 15.0 (Me); HRMS [ESI]: MH⁺, found 410.1957. $C_{24}H_{28}NO_5$ requires 410.1962.

4.2.3.4. 1'-Benzyl-5'-ethoxyspiro[cyclohex[2]ene-1,3'-indoline]-2',4-dione

To 1"-benzyl-5"-ethoxy-3'-hydroxydispiro[1,3-dioxolane-2,1'cyclohexane-4',3"-indol]-2"(1"H)-one 31 (0.261 g, 0.638 mmol) was added THF (3 mL) and 10% aqueous HCl solution (1.2 mL) and the mixture stirred at 70 °C for 90 min. The reaction mixture was allowed to cool to room temperature then quenched with sat. NaHCO₃ (6mL). The aqueous phase was extracted with EtOAc $(2 \times 5 \text{ mL})$. The combined organic phases were dried (MgSO₄), filtered and concentrated in vacuo. Purification by flash column chromatography (7:3 hexane/EtOAc) afforded the title compound (0.188 g, 85%) as a colourless oil; ν_{max} 2979, 1705, 1675, 1560, 1495, 1453, 1384, 1341 cm⁻¹; $\delta_{\rm H}$ (400 MHz; CDCl₃): 7.34-7.23 (5H, m), 6.80 (1H, d, J 2.4 Hz), 6.73 (1H, dd, J 8.4, 2.4 Hz), 6.67 (1H, d, J 8.4 Hz), 6.57 (1H, d, J 10.0 Hz), 6.27 (1H, d, J 10.0 Hz), 4.95 (1H, d, J 15.7 Hz), 4.85 (1H, d, J 15.7 Hz), 3.94 (2H, q, J 7.0 Hz), 3.16 (1H, ddd, J 17.2, 10.0, 5.3 Hz), 2.63 (1H, ddd, J 17.2, 6.9, 5.0 Hz), 2.51-2.42 (1H, m), 2.31 (1H, ddd, J 13.8, 10.0, 5.0 Hz), 1.36 (3H, t, J 7.0 Hz); δ_C (100 MHz, CDCl₃): 198.0 (C), 176.0 (C), 155.6 (C), 146.2 (CH), 135.5 (C), 135.4 (C), 132.5 (C), 131.6 (CH), 128.9 (CH), 127.8 (CH), 127.2 (CH), 113.8 (CH), 111.8 (CH), 110.1 (CH), 64.1 (CH₂), 50.1 (C), 44.1 (CH₂), 33.2 (CH₂), 32.3 (CH₂), 14.9 (Me); HRMS [ESI]: MH⁺, found 348.1588. C22H22NO3 requires 348.1594.

4.2.3.5. 1'-Benzyl-5'-ethoxyspiro[cyclohexane-1,3'indoline]-2',4-dione (12)

1'-benzyl-5'-To а stirred solution of ethoxyspiro[cyclohex[2]ene-1,3'-indoline]-2',4-dione (0.166 g, 0.478 mmol) in EtOAc (6.5 mL) was added 10 wt% Pd/C (21.7 mg). The vessel was placed under vacuum and back-filled with H₂ three times before being stirred at room temperature for 16 h under an atmosphere of H₂ (balloon). The reaction mixture was filtered through celite. The celite was washed with EtOAc (3×5 mL) then the combined organics were concentrated in vacuo. flash column chromatography Purification by (7:3)hexane/EtOAc) afforded the title compound 12 (0.162 g, 97%) as a colourless powder; m.p. 140–143 °C (Lit.⁵ 125–128 °C); v_{max} 3033, 2977, 2928, 1710, 1692, 1600, 1495, 1477, 1449, 1369, 1345 cm⁻¹; $\delta_{\rm H}$ (400 MHz; CDCl₃): 7.32-7.21 (5H, m), 6.84 (1H, d, J 2.5 Hz), 6.68 (1H, d, J 8.6 Hz), 6.62 (1H, d, J 8.6 Hz), 4.90 (2H, s), 3.94 (2H, q, J 6.9 Hz), 3.25-3.14 (2H, m), 2.58-2.44 (2H, m), 2.25-2.09 (4H, m), 1.36 (3H, t, J 6.9 Hz); δ_{C} (100 MHz, CDCl₃): 210.6 (C), 179.1 (C), 155.3 (C), 135.8 (C), 135.1 (C), 134.4 (C), 128.7 (CH), 127.6 (CH), 127.0 (CH), 112.5 (CH), 111.1 (CH), 109.6 (CH), 64.0 (CH₂), 45.8 (C), 43.5 (CH₂), 36.8 (CH₂), 33.7 (CH₂), 14.8 (Me); HRMS [ESI]: MH⁺, found 350.1741. C₂₂H₂₄NO₃ requires 350.1751.

4.2.4.1. N (4 Ethoxyphenyl) N [(4 methoxyphenyl)methyl] 7 oxo 1,4 dioxaspiro[4.5]decane 8 carboxamide (**33**)

To solution of $4 \Box$ ethoxy $\Box N \Box [(4 \Box$ а methoxyphenyl)methyl]aniline **32** (1.99 g, 7.75 mmol) and $7\Box$ $0x0 \square 1,4 \square dioxaspiro[4.5] decane \square 8 \square carboxylic acid 24 (3.10 g,$ 15.5 mmol) in EtOAc (77.5 mL) was added DIPEA (3.51 mL, 20.2 mmol) and T3P (50wt% in EtOAc, 9.86 g, 15.5 mmol). The reaction mixture was stirred at rt for 20 h, then diluted with EtOAc (50 mL), washed with H_2O (2 × 50 mL) and sat. brine (50 mL), dried over MgSO₄, filtered and concentrated in vacuo. Purification by flash column chromatography, eluting with EtOAc/hexane (1:4 to 1:1), afforded the title compound 33 (1.77 g, 52%) as a colourless solid; mp. 38-40 °C; v_{max} 2934, 2837, 1716, 1650, 1610, 1585, 1509, 1477, 1454, 1440, 1400, 1356, 1318, 1292, 1243, 1174, 1113, 1092, 1031 cm⁻¹; $\delta_{\rm H}$ (400 MHz; CDCl₃) 7.15 (2H, d, J 8.7 Hz), 6.82-6.73 (6H, m), 4.94 (1H, d, J 14.2 Hz), 4.67 (1H, d, J 14.2 Hz), 3.97 (2H, q, J 6.9 Hz), 3.96-3.87 (4H, m), 3.77 (3H, s), 3.19 (1H, dd, J 10.5 and 6.0 Hz), 2.68 (1H, dd, J 14.2 and 2.3 Hz), 2.32 (1H, d, J 13.7 Hz), 2.31-2.21 (1H, m), 2.08-2.02 (1H, m), 1.94-1.87 (1H, m), 1.72 (1H, ddd, J 12.8, 12.8, 4.5 Hz), 1.39 (3H, t, J 6.9 Hz); $\delta_{\rm C}$ (100 MHz; CDCl₃) 203.2 (C), 169.1 (C), 158.8 (C), 158.5 (C), 134.1 (C), 130.1 (CH), 129.5 (CH), 115.0 (CH), 113.6 (CH), 109.6 (C), 64.7 (CH₂), 64.6 (CH₂), 63.6 (CH₂), 55.2 (Me), 53.6 (CH), 52.5 (CH₂), 51.3 (CH₂), 33.0 (CH₂), 24.0 (CH₂), 14.7 (Me).; HRMS (ESI): MNa⁺, found 462.1874. C₂₅H₂₉NNaO₆ requires 462.1887.

4.2.4.2. 5'' Ethoxy 1'' [(4 methoxyphenyl)methyl] 1'',2'' dihydrodispiro[1,3 dioxolane 2,1' cyclohexane 4',3'' indole] 2'',5' dione (**34**)

In mesitylene: N \Box (4 \Box Ethoxyphenyl) \Box N \Box [(4 \Box methoxyphenyl)methyl] \Box 7 \Box oxo \Box 1,4 \Box dioxaspiro[4.5]decane \Box 8 \Box carboxamide **33** (0.659 g, 1.50 mmol) and Cu(OAc)₂·H₂O (29.9 mg, 10 mol%) in mesitylene (30 mL) was stirred at 165 °C with compressed air bubbled through for 20 min. Upon completion of the reaction, the mesitylene was removed under reduced pressure. Purification by flash column chromatography, eluting with EtOAc/Hexanes (1:4 to 2:3) afforded the title compound **34** (0.341 g, 52%) as a colourless oil.

In ethylene carbonate: $N \square (4 \square Ethoxyphenyl) \square N \square [(4 \square Ethoxyphenyl)]$ methoxyphenyl)methyl] \Box 7 \Box oxo \Box 1,4 \Box dioxaspiro[4.5]decane \Box 8 carboxamide 33 (0.650 g, 1.48 mmol) and Cu(2ethylhexanoate)₂ (53.0 mg, 10 mol%) in ethylene carbonate (15 mL) was stirred at 165 °C with compressed air bubbled through for 20 min. The reaction mixture was cooled to rt, then sat. NH₄Cl (30 mL) was added and the aqueous phase was extracted with EtOAc (3 \times 30 mL). The combined organics were washed with 10% NH₄OH solution (30 mL), H₂O (10 \times 30 mL) and sat. brine (30 mL), dried over MgSO₄, filtered and concentrated in vacuo. Purification by flash column chromatography, eluting with EtOAc/Hexanes (1:4 to 2:3) afforded the title compound 34 (0.265 g, 41%) as a colourless oil; mp 40–42 °C; v_{max} 2926, 1718, 1693, 1603, 1513, 1494, 1478, 1454, 1440, 1397, 1352, 1300, 1275, 1245, 1182, 1163, 1129, 1097, 1033, 1013 cm⁻¹; $\delta_{\rm H}$ (400 MHz; CDCl₃) 7.15 (2H, d, J 8.7 Hz), 6.84-6.80 (3H, m), 6.71 (1H, dd, J 8.7, 2.3 Hz), 6.61 (1H, d, J 8.7 Hz), 4.79 (2H, s), 4.07-3.92 (6H, m), 3.76 (3H, s), 3.53 (1H d, J 13.7 Hz), 2.83 (1H, ddd, J 12.9, 12.8, 4.6 Hz), 2.78 (1H, dd, J 13.7, 1.8 Hz), 2.26 (1H, ddd, J 13.7, 13.7, 4.6 Hz), 2.14 (1H, ddd, J 13.7, 4.6, 4.6 Hz), 2.00-1.94 (1H, m), 1.37 (3H, t, J 6.9 Hz); δ_C (100 MHz; CDCl₃) 200.8 (C), 173.1 (C), 159.0 (C), 155.4 (C), 135.6 (C), 129.9 (C), 128.4 (CH), 127.5 (C), 114.2 (CH), 113.9 (CH), 112.6 (CH),

109.7 (CH), 64.9 (CH₂), 64.7 (CH₂), 64.0 (CH₂), 62.5 (C), 55.2 (Me), 49.7 (CH₂), 43.3 (CH₂), 31.7 (CH₂), 30.4 (CH₂), 14.8 (Me).; HRMS (ESI): MNa⁺, found 460.1732. $C_{25}H_{27}NNaO_6$ requires 460.1731.

4.2.4.3. 5'' Ethoxy 5' hydroxy 1'' [(4 methoxyphenyl)methyl] 1'',2'' dihydrodispiro[1,3 dioxolane 2,1' cyclohexane 4',3'' indol] 2'' one (35)

To а solution of 5" \Box ethoxy \Box 1" \Box [(4 \Box methoxyphenyl)methyl] \Box 1",2" \Box dihydrodispiro[1,3 \Box dioxolane \Box 2,1' \Box cyclohexane \Box 4',3" \Box indole] \Box 2",5' \Box dione **34** (0.260 g, 0.594 mmol) in MeOH (5.9 mL) at 0 °C was added NaBH₄ (34.0 mg, 0.891 mmol) in one portion. The reaction mixture was stirred at 0 °C for 2 h, then quenched at the same temperature with sat. NH₄Cl (20 mL). The aqueous phase was extracted with EtOAc (3 \times 20 mL), and the combined organics were dried over MgSO₄, filtered, and concentrated in vacuo. Purification by flash column chromatography, eluting with EtOAc/Hexanes (1:1) afforded the title compound 35 (0.231 g, 89%) as a colourless solid; mp 54-56 °C; v_{max} 3448, 2932, 2885, 1691, 1596, 1513, 1489, 1440, 1345, 1290, 1245, 1177, 1144, 1110, 1049 cm⁻¹; $\delta_{\rm H}$ (400 MHz; CDCl₃) 7.17-7.14 (2H, m), 6.84-6.81 (3H, m), 6.71 (1H, dd, J 8.5, 2.5 Hz), 6.61 (1H, d, J 8.5 Hz), 4.79 (2H, s), 4.05-3.92 (6H, m), 3.76 (3H, s), 3.52 (1H, d, J 13.6 Hz), 2.83 (1H, td, J 12.9, 5.0 Hz), 2.79 (1H, dd, J 13.4, 1.9 Hz), 2.26 (1H, td, J 13.2, 4.4 Hz), 2.14 (1H, dt, J 13.8, 4.4 Hz), 1.99-1.94 (1H, m), 1.37 (3H, t, J 7.0 Hz); δ_C (100 MHz; CDCl₃) 177.0 (C), 157.7 (C), 153.6 (C), 127.1 (CH), 126.8 (C), 113.2 (CH), 112.9 (CH), 111.4 (CH), 108.0 (CH), 107.6 (C), 70.0 (C), 63.3 (CH₂), 63.2 (CH₂), 62.8 (CH₂), 54.0 (Me), 41.9 (CH₂), 28.8 (CH₂), 27.1 (CH₂), 13.7 (Me); HRMS (ESI): MNa⁺, found 462.1870. C₂₅H₂₉NNaO₆ requires 462.1887.

4.2.4.4. 5'' Ethoxy 1'' [(4 methoxyphenyl)methyl] 1'',2'' dihydrodispiro[1,3 dioxolane 2,1' cyclohexane 4',3'' indol] 2' en 2'' one

 $5" \Box$ ethoxy $\Box 5' \Box$ hydroxy $\Box 1" \Box [(4 \Box$ А solution of methoxyphenyl)methyl] 1",2" dihydrodispiro[1,3 dioxolane 2,1'□cyclohexane□4',3"□indol]□2"□one **35** (0.210 g, 0.478 mmol) in THF (2.4 mL) and 10% HCl (0.96 mL) was heated at reflux for 2 h. After cooling to rt, the reaction mixture was partitioned between sat. NaHCO3 (25 mL) and EtOAc (3 \times 25 mL). The combined organics were dried over MgSO₄, filtered, and concentrated in vacuo. Purification by flash column chromatography, eluting with EtOAc/Hexanes (1:4 to 1:3) afforded the title compound (0.156 g, 87%) as a colourless solid; mp 142–143 °C; v_{max} 2979, 2932, 1697, 1674, 1611, 1599, 1513, 1493, 1476, 1443, 1384, 1335, 1290, 1275, 1245, 1221, 1176, 1109, 1033 cm⁻¹; δ_H (400 MHz; CDCl₃) 7.22 (2H, d, J 8.7 Hz), 6.85 (2H, d, J 8.7 Hz), 6.80 (1H, d, J 2.8 Hz), 6.75 (1H, dd, J 8.2, 2.3 Hz), 6.70 (1H, d, J 8.2 Hz), 6.51 (1H, d, J 10.1 Hz), 6.28 (1H, d, J 10.1 Hz), 4.89 (1H, d, J 15.1 Hz), 4.79 (1H, d, J 15.1 Hz), 3.95 (2H, q, J 6.9 Hz), 3.78 (3H, s), 3.17 (1H, ddd, J 17.0, 10.1, 5.0 Hz), 2.63 (1H, ddd, J 17.4, 6.9, 5.0 Hz), 2.49-2.42 (1H, m), 2.30 (1H, ddd, J 14.6, 9.6, 5.0 Hz), 1.38 (3H, t, J 6.9 Hz); HRMS (ESI): MNa⁺, found 400.1511. C₂₃H₂₃NNaO₄ requires 400.1519.

4.2.4.5. 5" Ethoxy 1" [(4

methoxyphenyl)methyl] 1",2"

dihydrodispiro[1,3 dioxolane 2,1' cyclohexane 4',3'' indol] 2'' one (**36**)

To a stirred solution of 5" = thoxy = 1" = [(4 = methoxyphenyl)methyl] = 1",2" = dihydrodispiro[1,3 = dioxolane = 2,1' = cyclohexane = 4',3" = indol] = 2' = n = 2" = one (0.145 g, 0.384)

mmol) in EtOAc (3.8 mL) was added 10% Pd/C (77 mg). The M vessel was placed under vacuum and back-filled with H₂ four times before being stirred at room temperature for 18 h under an atmosphere of H₂. The reaction mixture was filtered through celite. The celite was washed with EtOAc (2×15 mL) then the combined organics concentrated in vacuo to afford the title compound 36 (0.143 g, 96%) as a colourless solid; mp 123-125 °C; v_{max} 2978, 2929, 1711, 1691, 1600, 1513, 1494, 1477, 1443, 1395, 1368, 1343, 1291, 1274, 1245, 1177, 1110, 1044, 1033. cm⁻¹; $\delta_{\rm H}$ (400 MHz; CDCl₃) 7.21 (2H, d, J 8.7 Hz), 6.87-6.82 (3H, m), 6.70 (1H, dd, J 8.7, 1.8 Hz), 6.67 (1H, d, J 8.7 Hz), 4.85 (2H, s), 3.96 (2H, q, J 7.3 Hz), 3.77 (3H, s), 3.21 (2H, ddd, J 16.0, 10.5, 6.4 Hz), 2.50 (2H, ddd, J 14.7, 4.6, 4.6 Hz), 2.24-2.11 (4H, m), 1.38 (3H, t, J 6.9 Hz); δ_C (100 MHz; CDCl₃) 210.7 (C), 178.9 (C), 159.1 (C), 155.3 (C), 135.2 (C), 134.5 (C), 128.5 (CH), 127.9 (C), 114.2 (CH), 112.6 (CH), 111.1 (CH), 109.6 (CH), 64.1 (CH₂), 55.2 (Me), 45.8 (C), 43.0 (CH₂), 36.9 (CH₂), 33.7 (CH₂), 14.8 (Me).; HRMS (ESI): MNa⁺, found 402.1680. C₂₃H₂₅NNaO₄ requires 402.1676.

4.2.4.6. 5' Ethoxy 4 hydroxy 1' [(4 methoxyphenyl)methyl] 1',2' dihydrospiro[cyclohexane 1,3' indol] 2' one (37)

To solution of $5" \Box$ ethoxy $\Box 1" \Box [(4 \Box$ а methoxyphenyl)methyl] \Box 1",2" \Box dihydrodispiro[1,3 \Box dioxolane \Box 2,1' \Box cyclohexane \Box 4',3" \Box indol] \Box 2" \Box one **36** (0.140 g, 0.369 mmol) in THF (2 mL) at -78 °C was added L-Selectride (1.0 M in THF, 0.55 mL, 0.550 mmol). The reaction mixture was stirred at -78 °C for 2 h, then quenched at the same temperature by the addition of H₂O (20 mL). The aqueous phase was extracted with EtOAc (3 \times 20 mL), and the combined organics dried over MgSO₄, filtered, and concentrated in vacuo. Purification by flash column chromatography, eluting with EtOAc/Hexanes (1:1) afforded the title compound 37 (0.119 g, 84%) as a colourless oil; v_{max} 3406, 2925, 2855, 1688, 1612, 1598, 1513, 1495, 1476, 1442, 1393, 1365, 1341, 1289, 1273, 1245, 1177, 1109, 1050, 1035 cm⁻¹; δ_H (400 MHz; CDCl₃) 7.18 (2H, d, J 8.2 Hz), 6.85-6.81 (3H, m), 6.65 (1H, dd, J 8.7, 2.3 Hz), 6.59 (1H, d, J 8.2 Hz), 4.80 (2H, s), 3.95 (2H, q, J 6.9 Hz), 3.98-3.87 (1H, m), 3.76 (3H, s), 2.28-2.18 (2H, m), 2.05-1.94 (4H, m), 1.74-1.66 (2H, m), 1.37 (3H, t, J 6.9 Hz); δ_C (100 MHz; CDCl₃) 179.7 (C), 158.8 (C), 155.0 (C), 135.9 (C), 135.1 (C), 128.4 (CH), 128.2 (C), 114.0 (CH), 112.0 (CH), 111.1 (CH), 109.1 (CH), 68.8 (CH), 64.0 (CH₂), 55.1 (Me), 46.1 (C), 42.7 (CH₂), 31.1 (CH₂), 29.6 (CH₂), 14.8 (Me).; HRMS (ESI): MNa⁺, found 404.1822. C₂₃H₂₇NNaO₄ requires 404.1832.

4.2.4.7. 5' Ethoxy 1' [(4 methoxyphenyl)methyl] 4 (prop 2 yn 1 yloxy) 1',2' dihydrospiro[cyclohexane 1,3' indol] 2' one (**38**)

solution of 5' = thoxy = 4 = hydroxy = 1' = [(4 = 1) + 1] = [(4 = 1) + 1]To а methoxyphenyl)methyl] \Box 1',2' \Box dihydrospiro[cyclohexane \Box 1,3' \Box indol] 2' one 37 (0.091 g, 0.239 mmol) in THF (3 mL) was added NaH (60% in mineral oil, 0.038 g, 0.956 mmol) in one portion. The reaction mixture was heated at reflux for 1 h before the addition of propargyl bromide (106 µL, 0.717 mmol). Stirring was maintained at reflux for a further 17 h. After cooling to rt, the reaction mixture was partitioned between sat. NH₄Cl (20 mL) and EtOAc (3×20 mL). The combined organics were dried over MgSO₄, filtered, and concentrated in vacuo. Purification by flash column chromatography, eluting with EtOAc/Hexanes (1:9 to 1:1) afforded the title compound (0.077 g, 77%) as a colourless oil; v_{max} 3226, 2978, 2941, 2114, 1689, 1611, 1594, 1513, 1485, 1475, 1457, 1438, 1387, 1369, 1340, 1318, 1300, 1287, 1270, 4248, **E187**, **E1176**, 1153, 1130, 1114, 1102, 1088, 1069, 1052, 1034, 1011 cm⁻¹; $\delta_{\rm H}$ (400 MHz; CDCl₃) 7.18 (2H, d, *J* 8.7 Hz), 6.88 (1H, d, *J* 2.3 Hz), 6.83 (2H, d, *J* 8.7 Hz), 6.65 (1H, dd, *J* 8.7, 2.3 Hz), 6.59 (1H, d, *J* 8.7 Hz), 4.80 (2H, s), 4.26 (2H, d, *J* 2.3 Hz), 3.95 (2H, q, *J* 6.9 Hz), 3.87-3.79 (1H, m), 3.76 (3H, s), 2.43 (1H, t, *J* 2.3 Hz), 2.28-2.20 (2H, m), 2.06-1.95 (4H, m), 1.67-1.61 (2H, m), 1.38 (3H, t, *J* 6.9 Hz); $\delta_{\rm C}$ (100 MHz; CDCl₃) 179.8 (C), 159.0 (C), 155.0 (C), 136.1 (C), 135.4 (C), 128.6 (CH), 128.4 (C), 114.2 (CH), 112.0 (CH), 111.7 (CH), 109.2 (CH), 80.5 (C), 74.4 (CH), 74.0 (C), 64.1 (CH₂), 55.3 (Me), 55.0 (CH₂), 46.6 (C), 43.0 (CH₂), 30.7 (CH₂), 26.0 (CH₂), 15.0 (Me).; HRMS (ESI): MNa⁺, found 442.1980. C₂₆H₂₉NNaO₄ requires 442.1989.

4.2.4.8. 4-[(1-Benzyl-1H-1,2,3-triazol-4yl)methoxy]-5'-ethoxy-1'-[(4methoxyphenyl)methyl]-1,2'dihydrospiro[cyclohexane-1,3'-indole]-2'-one (**39**)

To a solution of 5' ethoxy $1' [(4 \\ methoxyphenyl)methyl] 4 [(prop 2] yn] 1] yloxy) 1',2']$

dihydrospiro[cyclohexane]1,3'[indol]2'[one 38 (30.0 mg, 0.072 mmol) in THF (2 mL) was added benzyl azide (14 µL, 0.108 mmol), CuI (2.7 mg, 14.4 µmol) and DIPEA (25 µL, 0.144 mmol). The reaction mixture was stirred at rt for 22 h, then partitioned between H₂O (20 mL) and EtOAc (3×20 mL). The combined organics were dried over MgSO₄, filtered, and concentrated in vacuo. Purification by flash column chromatography, eluting with EtOAc/Hexanes (1:4 to 2:3) afforded the title compound **39** (40.2 mg, quant.) as a colourless solid; mp 148–150 °C; v_{max} 2928, 2865, 1694, 1603, 1510, 1493, 1449, 1364, 1335, 1289, 1271, 1244, 1172, 1109, 1051, 1032 cm⁻ ¹; $\delta_{\rm H}$ (400 MHz; CDCl₃) 7.54 (1H, s), 7.40-7.34 (3H, m), 7.30-7.28 (2H, m), 7.19-7.15 (2H, m), 6.86 (1H, d, J 2.4 Hz), 6.84-6.80 (2H, m), 6.64 (1H, dd, J 8.5, 2.4 Hz), 6.58 (1H, d, J 8.5 Hz), 5.52 (2H, s), 4.79 (2H, s), 4.72 (2H, s), 3.95 (2H, q, J 7.0 Hz), 3.75 (3H, s), 3.73-3.69 (1H, m), 2.27-2.18 (2H, m), 2.06-1.93 (4H, m), 1.65-1.60 (2H, m), 1.38 (3H, t, *J* 7.0 Hz); δ_C (100 MHz; CDCl₃) 179.8 (C), 159.0 (C), 155.0 (C), 146.8 (C), 136.1 (C), 135.4 (C), 134.8 (C), 129.2 (CH), 128.8 (CH), 128.6 (CH), 128.4 (C), 128.2 (CH), 122.4 (CH), 114.2 (CH), 112.1 (CH), 111.6 (CH), 109.2 (CH), 75.5 (CH), 64.1 (CH₂), 61.9 (CH₂), 55.3 (Me), 54.2 (CH₂), 46.6 (C), 42.9 (CH₂), 30.8 (CH₂), 26.3 (CH₂), 15.0 (Me); HRMS (ESI): MNa^+ , found 575.2612. $C_{33}H_{36}N_4NaO_4$ requires 575.2629.

4.2.4.9. 4 [(1 Benzyl 1H 1,2,3 triazol 4 yl)methoxy] 5' ethoxy 1',2' dihydrospiro[cyclohexane 1,3' indol] 2' one (40)

A solution of 4-[(1-benzyl-1H-1,2,3-triazol-4-yl)methoxy]-5'ethoxy-1'-[(4-methoxyphenyl)methyl]-1,2'dihydrospiro[cyclohexane-1,3'-indole]-2'-one 39 (33.7 mg, 0.061 mmol) in TFA (3 mL) was heated at reflux for 2 d. After cooling to rt, the reaction mixture was partitioned between sat. NaHCO₃ (35 mL) and CH_2Cl_2 (3 × 35 mL). The combined organics were dried over MgSO₄, filtered, and concentrated in vacuo. Purification by flash column chromatography, eluting with EtOAc/Hexanes (1:1) afforded the title compound (23.5 mg, 89%) as a colourless solid; mp 70–72 °C; v_{max} 3211, 2925, 2854, 1697, 1603, 1494, 1456, 1392, 1364, 1328, 1307, 1245, 1196, 1112, 1081, 1047 cm⁻¹; $\delta_{\rm H}$ (400 MHz; CDCl₃) 8.41 (1H, br s), 7.53 (1H, s), 7.38-7.34 (2H, m), 7.3-7.28 (2H, m), 6.83 (1H, d, J 2.4 Hz), 6.79 (1H, d, J 8.5 Hz), 6.70 (1H, dd, J 8.4, 2.5 Hz), 5.53 (2H, s), 4.72 (2H, s), 3.98 (2H, q, J 7.0 Hz), 3.72-3.66 (1H, m), 2.22-2.14 (2H, m), 2.03-1.94 (4H, m), 1.63-1.57 (2H, m), 1.40 (3H, t, J 7.0 Hz).; δ_C (100 MHz; CDCl₃) 182.5 (C), 154.9 (C), 146.7 (C), 136.6 (C), 134.7 (C), 133.4 (C), 129.2 (CH), 128.8 (CH), 128.3 (CH), 122.5 (CH), 112.5 (CH), 141.5 (CH), 109.9 MAN 2.5 (CH), 75.5 (CH), 64.2 (CH₂), 61.9 (CH₂), 54.3 (CH₂), 47.1 (C), 30.6 (CH₂), 26.2 (CH₂), 15.0 (Me); HRMS (ESI): MNa⁺, found 455.2040. $C_{25}H_{28}N_4NaO_3$ requires 455.2054.

4.2.4.10.4 [(1 benzyl 1H 1,2,3 triazol 4 yl)methoxy] 1' [2 chloro 4 (trifluoromethyl)benzenesulfonyl] 5' ethoxy 1',2' dihydrospiro[cyclohexane 1,3' indol] 2' one (41)

To a solution of $4 \square [(1 \square benzyl \square 1H \square 1,2,3 \square triazol \square 4 \square$ yl)methoxy] 5' ethoxy 1',2' dihydrospiro[cyclohexane 1,3'□indol]□2'□one 40 (20.6 mg, 0.048 mmol) in THF (1.5 mL) at 0 °C was added KOt-Bu (16.2 mg, 0.144 mmol). The reaction mixture was stirred at rt for 20 min before the addition of 2chloro-4-(trifluoromethyl)benzenesulfonyl chloride (40.2 mg, 0.144 mmol). Stirring was continued at rt for 16 h, then sat. NH₄Cl (15 mL) was added. The aqueous phase was extracted with EtOAc (3 \times 15 mL), dried over MgSO₄, filtered, and concentrated in vacuo. Purification by flash column chromatography, eluting with EtOAc/Hexanes (1:1) afforded the title compound 41 (17.4 mg, 54%) as a colourless solid; mp 56-58 °C; ν_{max} 2980, 2933, 1746, 1690, 1594, 1487, 1471, 1393, 1371, 1321, 1289, 1247, 1228, 1177, 1142, 1116, 1080, 1043 cm⁻ ¹; $δ_{\rm H}$ (400 MHz; CDCl₃) 8.46 (1H, d, J 8.1 Hz), 7.78-7.73 (3H, m), 7.43 (1H, s), 7.39-7.34 (3H, m), 7.28-7.25 (2H, m), 6.83 (1H, dd, J 8.9, 2.6 Hz), 6.78 (1H, d, J 2.6 Hz), 5.50 (2H, s), 4.03 (2H, q, J 7.0 Hz), 3.61-3.55 (1H, m), 1.94-1.88 (6H, m), 1.67-1.59 (2H, m), 1.43 (3H, t, J 7.0 Hz); δ_C (100 MHz; CDCl₃) 177.7 (C), 156.7 (C), 146.4 (C), 139.6 (C), 136.5 (C, q, J 34.0 Hz), 134.6 (C), 134.5 (C), 134.1 (CH), 133.4 (C), 131.4 (C), 129.2 (CH), 128.9 (CH), 128.8 (CH, q, J 3.9 Hz), 128.2 (CH), 124.2 (CH, q, J 3.7 Hz), 122.4 (C, q, J 272 Hz), 122.3 (CH) 115.1 (CH), 113.3 (CH), 110.4 (CH), 75.3 (CH), 64.0 (CH₂), 61.7 (CH₂), 54.3 (CH₂), 46.4 (C), 31.8 (CH₂), 26.1 (CH₂), 14.9 (Me); HRMS (ESI): MNa⁺, found 697.1477. $C_{32}H_{30}^{35}ClF_3NNaO_5S$ requires 697.1470.

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References

 Lee, J. J. Y.; Kilonzo, K.; Nistico, A.; Yeates, K. Can. Med. Assoc. J. 2014, 186, E281-E286. b) Henry, D. A. Ann. Intern. Med. 2015, 163, ITC1-ITC15.

- Torres, V. E.; Chapman, A. B.; Devuyst, O.; Gansevoort, R. T.; Grantham, J. J.; Higashihara, E.; Perrone, R. D.; Krasa, H. B.; Ouyang, J.; Czerwiec, F. S. *New. Eng. J. Med.* 2012, *367*, 2407– 2418. b) Shoaf, S. E.; Elizari, M. V.; Wang, Z.; Sekar, K.; Grinfeld, L. R.; Barbagelata, N. A.; Lerman, J.; Bramer, S. L.; Trongé, J.; Orlandi, C. *J. Cardiovasc. Pharmacol. Therapeut.* 2005, 10, 165–171. c) Gheorghiade, M.; Gattis, W. A.; O'Connor, C. M.; Adams, Jr, K. F.; Elkayam, U.; Barbagelata, A.; Ghali, J. K.; Benza, R. L.; McGrew, F. A.; Klapholz, M.; Ouyang, J.; Orlandi, C. *J. Amer. Med. Assoc.* 2004, *291*, 1963–1971.
- Loïc Foulon, P.; Georges Garcia, F.; Claudine Serradeil-Le Gal, E.; Gérard Valette, L.-F. US Patent 5 994 350, 1999.
- 5. Venkatesan, H.; Davis, M. C.; Altas, Y.; Snyder, J. P.; Liotta, D. C. J. Org. Chem. 2001, 66, 3653-3661.
- a) Lanza, T.; Minozzi, M.; Monesi, A.; Nanni, D.; Spagnolo, P.; Zanardi, G. Adv. Synth. Catal. 2010, 352, 2275–2280. b) González-López de Turiso, F.; Curran, D. P. Org. Lett. 2005, 7, 151–154.
- a) Hayashi, K.; Takayama, J.; Xuan, M.; Suda, M.; Teramae, H.; Sakamoto, T. Heterocycles, **2016**, *92*, 1785–1795. b) Yu, Z.; Ju, X.; Wang, J.; Yu, W. Synthesis **2011**, 860–866.
- Sánta-Csutor, A.; Mucsi, Z.; Finta, Z.; Gönczi, C.; Halász, J.; Csikós, E.; Hermecz, I. *Eur. J. Org. Chem.* **2006**, 1769–1778. b) Hermecz, I.; Sánta-Csutor, A.; Gönczi, C.; Héja, G.; Csikós, E.; Simon, K.; Smelkó-Esek, A.; Podányi, B. *Pure. Appl. Chem.* **2001**, *73*, 1401–1409.
- a) Perry, A.; Taylor, R. J. K. Chem. Commun. 2009, 3249–3251.
 b) Moody, C. L.; Franckevičius, V.; Drouhin, P.; Klein, J. E. M. N.; Taylor, R. J. K. Tetrahedron Lett. 2012, 53, 1897–1899. c) Hurst, T. E.; Gorman, R.; Drouhin, P.; Perry, A.; Taylor, R. J. K. Chem. Eur. J. 2014, 20, 14063-14073. d) Drouhin, P.; Hurst, T. E.; Whitwood, A. C.; Taylor, R. J. K. Org. Lett. 2014, 16, 4900–4903. e) Drouhin, P.; Hurst, T. E.; Whitwood, A. C.; Taylor, R. J. K. Tetrahedron 2015, 71, 7124–7136.
- For a related copper-based approach see: a) Dey, C.; Larinov, E.; Kündig, E. P. *Org. Biomol. Chem.* **2013**, *11*, 6735–6743 and references therein. For other approaches see: b) Donald, J. R.; Taylor, R. J. K.; Petersen, W. F. *J. Org. Chem.* **2017**, *82*, 11288– 11294. c) Wu, Z.-J.; Xu, H.-C. *Angew. Chem. Int. Ed.* **2017**, *56*, 4734–4738.
- 11. Sparrow, K.; Barker, D.; Brimble, M. A. *Tetrahedron* **2012**, *68*, 1017–1028.
- Standard hydrolysis under basic conditions led to poor and irreproducible yields of product due to extensive decomposition of the starting material.
- 13. Barton., D. H. R.; Motherwell, W. B.; Strange, A. Svnthesis 1981 743-744.
- (a) Wissmann, H.; Kleiner, H.-J. *Angew. Chem. Int. Ed.* 1980, *19*, 133–134;
 (b) For recent applications see Unsworth, W. P.; Kitsiou, C.;

Taylor, R. J. K. *Org. Lett.* **2013**, *15*, 258–261; Unsworth, W. P.; Gallagher, K. A.; Jean, M.; Schmidt, J. P.; Diorazio, L. J.; Taylor, R. J. K. *Org. Lett.* **2013**, *15*, 262–265.

 Parker, H. L.; Sherwood, J.; Hunt, A. J.; Clark, J. H. ACS Sustainable Chem. Eng. 2014, 2, 1739–1742; for a recent review on green solvents see Clarke, C. J.; Tu, W.-C.; Levers, O.; Bröhl, A.; Hallett, J. P. Chem. Rev. 2018, 118, 747–800.

Palm, C.; Pistrosch, F.; Herbrig, K.; Gross, P. Am. J. Med. 2006, 119, S87-S92.