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Divergent approach to the polymaxenolide and pinnaic acid cores

Frank D. Ferrari [a], Andrew J. Ledgard [b], Rodolfo Marquez [a,*,†]

[a] WestChem, School of Chemistry, University of Glasgow, Glasgow, G12 8QQ, Scotland, UK
[b] Lilly Research Centre, Erl Wood Manor Windlesham, Surrey, GU20 6PH, UK

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ABSTRACT

The divergent syntheses of the spirocyclic pyran core of polymaxenolide and the spirocyclic piperidine core of pinnaic acid have been achieved. Our divergent approach takes advantage of highly efficient Achmatowicz and aza-Achmatowicz rearrangements to generate the highly functionalised cores, which are then regioselectively modified.

1. Introduction

Polymaxenolide **1**, was isolated in 2004 from the hybrid soft coral *Sinularia maxima x Sinularia polydactyla* in the Piti bomb holes in Guam.[1] Polymaxenolide **1** is the product of a mixed biosynthetic pathway, and structurally comprises a unique hybrid cembrane–africanane joined skeleton through a beautifully defined spirocyclic pyran from which a large degree of functionality is appended.

Polymaxenolide **1** is the first example of a hybrid metabolite from marine origin. From a biological point of view, the mixed biosynthetic origin of polymaxenolide makes it a very enigmatic compound. In terrestrial metabolites, 18% of the hybrid species isolated thus far exhibit different chemical and biological properties from the parental species.[2] This differential behaviour makes the hybrid compounds important new starting materials for the development of diversity-orientated synthesis and libraries.

The exciting combination of therapeutic potential, together with a highly challenging molecular framework makes polymaxenolide **1** a very attractive and interesting synthetic target. However, despite its potential and attractive structure, no total syntheses of polymaxenolide have been reported to date (Fig. 1).

A nitrogenous analogue of the spirocyclic pyran core of polymaxenolide **1** is displayed by pinnaic acid **2**, tauropinnaic acid **3** and halichlorine **4**.

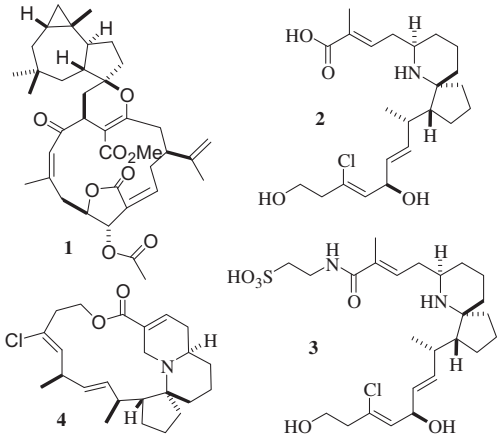

Fig. 1. Polymaxenolide **1**, Pinnaic acid **2**, tauropinnaic acid **3** and halichlorine **4**.

Pinnaic acid **2** and tauropinnaic acid **3** were isolated in minute amounts from the Okinawan bivalve *Pinna muricata* by Uemura and co-workers (1 mg and 4 mg were isolated from 10 kg of bivalve, respectively).[3] Biologically, pinnaic acid **2** and tauropinnaic acid **3** have been shown to inhibit cytosolic phospholipase A_2 ($cPLA_2$) at low micromolar concentrations (200 μM and 90 μM, respectively), making them promising leads for the treatment of pro-inflammatory diseases.[3b,4]

A number of total and formal syntheses of pinnaic acid **2**, tauropinnaic acid **3** and halichlorine **4** employing widely diverse and creative synthetic approaches and methodologies have been

* Corresponding author. Tel.: +44 0141 330 5953; fax: +44 0141 330 488; e-mail address: r.marquez@chem.gla.ac.uk (R. Marquez).
† Ian Sword Lecturer of Organic Chemistry.

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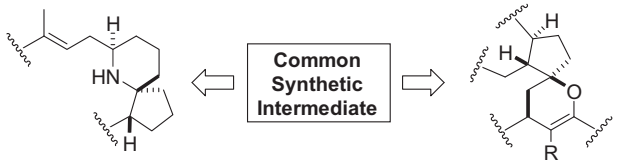
reported.[5,6] However, none of the approaches developed are readily applicable to the synthesis of the spirocyclic pyran core of polymaxenolide **1.**

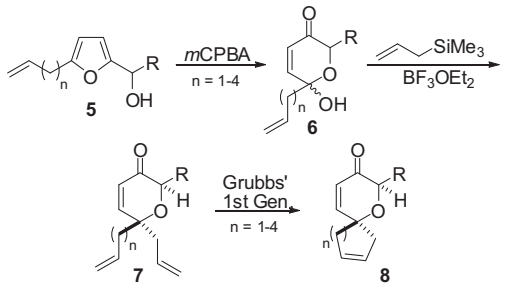
The similar structural features present in the spirocyclic cores of polymaxenolide **1**, pinnaic acid **2**, tauropinnaic acid **3** and halichlorine **4**, however made us to consider the possibility that a divergent synthetic approach could be used to quickly and efficiently generate both the spirocyclic piperidine and spirocyclic pyran cores from a common synthetic intermediate (Scheme 1).



Scheme 1.

2. Results and discussion

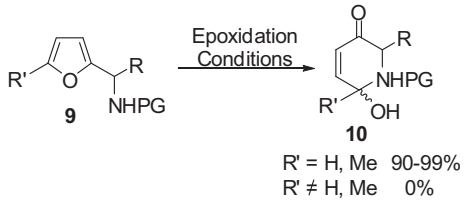
We previously reported the use of 2,5-disubstituted furan rings **5** to generate pyran units **6** via the highly effective Achmatowicz rearrangement.[7] Significantly, the rearrangement proceeded cleanly and efficiently to afford the desired lactols **6** in the presence of various functionalities including olefins without detrimental effect (Scheme 2).



Scheme 2.

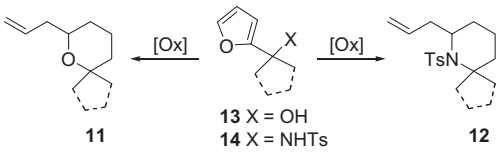
Lewis-acid promoted allylation of the lactol units yielded the desired bis-olefins **7** in good yield and more importantly as single diastereomers. The stereochemistry of the allylation and consequently, that of the newly formed C6 stereocentre was dictated by that of the C2 carbon in complete consistency with Woerpel's model.[8] Ring closing metathesis of the bis-alkenes **7** afforded the desired spirocyclic pyrans **8** as single diastereomers.

Having successfully generated the desired spirocyclic pyrans, **8** it was decided to apply this approach to the synthesis of spirocyclic piperidines. Unfortunately, the aza-Achmatowicz[9] rearrangement of the furfuryl amine precursors **9** proved to be extremely temperamental, and highly dependent on the nature of the C5 furan substituent (i.e., whilst most groups were tolerated alpha to the furfuryl amine, anything other than a methyl substituent or an unsubstituted C5 furan position failed to yield any of the desired hemi-aminals **10**) (Scheme 3).



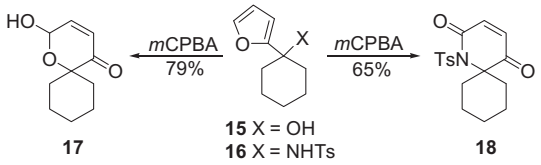
Scheme 3.

Faced with an unreliable approach to the synthesis of the hemiaminal intermediate **10**, a new strategy to the synthesis of the spirocyclic core was devised. In our modified approach, the spiropyran **11** and spirocyclic piperidine **12** cores were envisioned as having originated from the oxidative rearrangement of the cyclic tertiary furfuryl alcohol **13** and the cyclic tertiary amine **14**, respectively. If successful, this approach should provide us with a rapid and efficient route to the synthesis of the polymaxenolide and pinnaic acid core structures (Scheme 4).



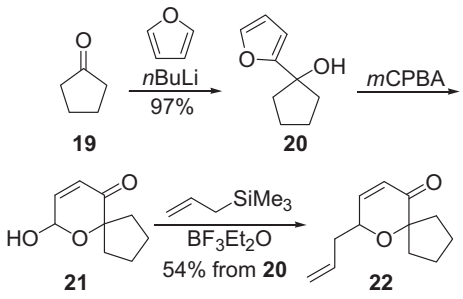
Scheme 4.

This approach was inspired by the work of Couladouros and coworkers who reported the oxidative rearrangement of a cyclohexylfuryl carbinol **15** to generate the pyranone **17**. The analogous tosylamine **16** however, failed to generate any of the desired azapyranone, yielding instead the spirolactam unit **18** (Scheme 5).[10]



Scheme 5.

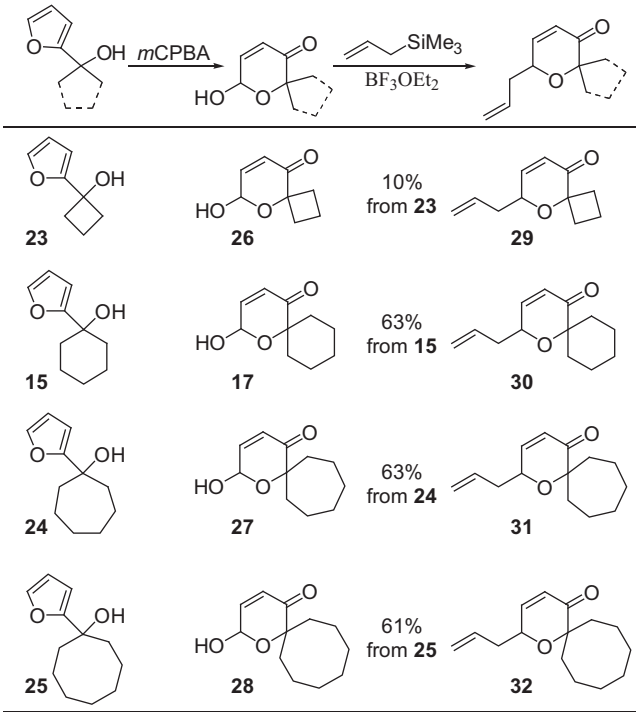
However, despite this somewhat mixed precedent, we were confident that through modification of the oxidative rearrangement conditions it would be possible to generate both the pyranone and azapyranone units whilst avoiding the undesired overoxidation. Our initial model studies began with cyclopentanone **19**, which was treated with 2-lithiofuran to generate furfuryl alcohol **20**. As expected, treatment of carbinol **20** under our previously used Achmatowicz oxidative conditions yielded the desired lactol **21** in good yield. Boron trifluoride promoted allylation of lactol **21** with allyltrimethylsilane afforded the polyfunctionalised [5.4] spirocyclic pyran **22** unit in high yield over the three step sequence (Scheme 6).



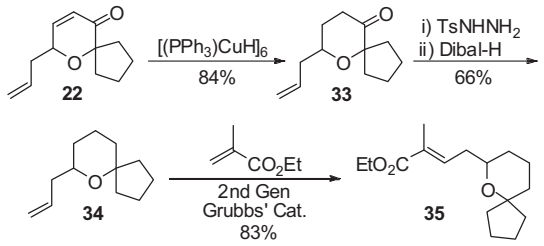
Scheme 6.

The reaction sequence was then applied successfully to generate the corresponding [5.3], [5.5], [5.6] and [5.7] spirocyclic pyrans. Interestingly, all of them proceed in good yield over the entire synthetic process with the exception of the highly strained [5.3] spirocyclic unit, which yielded a complex mixture from which the desired spirocyclic pyran unit was isolated in low yield (Table 1).

Table 1
Synthesis of Spirocyclic Pyrans.



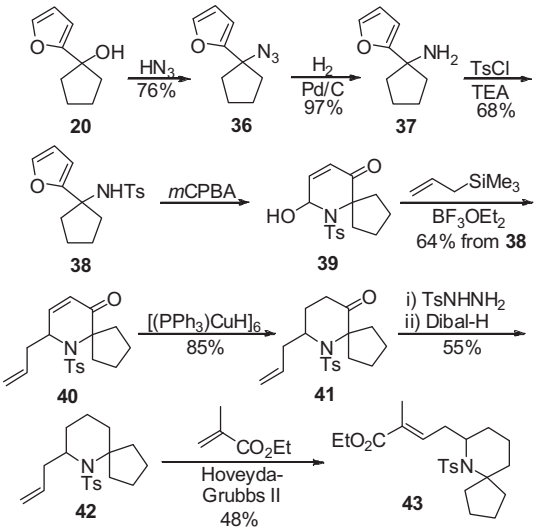
Having successfully generated the desired spirocyclic pyran cores, the regiospecific modification of the functionality within the pyran unit was investigated. Thus, selective 1,4-reduction of enone **22** with Stryker's reagent afforded ketone **33**.[11] Interestingly, all other reduction conditions attempted resulted in either the over-reduction of the enone unit or in the loss of the terminal alkene unit. Tosylhydrazone mediated reduction of ketone **33**[9a] then gave the fully saturated pyran unit **34**, which upon cross metathesis with ethyl methacrylate yielded the trisubstituted conjugated methyl ester **35** as a single regio-isomer (Scheme 7).[6d]



Scheme 7.

Having demonstrated the ability of cyclic tertiary carbinols to generate spirocyclic pyrans quickly and efficiently, the synthesis of the key cyclic tertiary amines was investigated. After much experimentation, we are pleased to report that the treatment of furfuryl alcohol **20** with hydrazoic acid yielded the desired azide **36**, which was then reduced efficiently in good yield (Scheme 8).[10]

Tosyl protection of the newly formed tertiary amine yielded the cyclisation precursor **38**, which upon treatment with *m*-CPBA afforded the key hemi-aminal **39**. Allylation of hemi-aminal **39** under Lewis-acid promoted conditions gave the desired spirocyclic piperidine **40** in good yield.[12] As in the case of the spirocyclic pyran series, selective 1,4-reduction could be achieved using Stryker's reagent to afford piperidone **41**. Piperidone deoxygenation then produced the desired spirocyclic piperidine **42** in good yield over



Scheme 8.

the two steps. Finally, cross metathesis of alkene **42** with ethyl methacrylate proceeded in reasonable yield to afford the pinnaic acid core structure **43** as a single *E* double bond isomer.

In conclusion, we have developed a flexible and divergent approach to the synthesis of spirocyclic pyrans and spirocyclic piperidines starting from a common cyclic tertiary carbinol precursor. We believe that this approach is efficient and provides rapid entry to differentially functionalised spirocyclic structures. Efforts in our group are focused currently in the application of this methodology to the total synthesis of polymaxenolide and pinnaic acid.

3. Experimental

3.1. General

All reactions were performed in oven-dried glassware under an inert argon atmosphere unless otherwise stated. Tetrahydrofuran (THF), diethyl ether and dichloromethane (DCM) were purified through a Pure Solv 400-5MD solvent purification system (Innovative Technology, Inc). All reagents were used as received, unless otherwise stated. Solvents were evaporated under reduced pressure at 40 °C using a Buchi Rotavapor.

IR spectra were recorded as thin films on NaCl plates using a JASCO FT/IR410 Fourier Transform spectrometer. Only significant absorptions (ν_{max}) are reported in wavenumbers (cm^{-1}). Proton magnetic resonance spectra (^1H NMR) and carbon magnetic resonance spectra (^{13}C NMR) were, respectively, recorded at 400 MHz and 100 MHz using a Bruker DPX Avance400 instrument. Chemical shifts (δ) are reported in parts per million (ppm) and are referenced to the residual solvent peak. The order of citation in parentheses is (1) number of equivalent nuclei (by integration), (2) multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad, dm=double multiplet), and (3) coupling constant (*J*) quoted in hertz to the nearest 0.5 Hz. High resolution mass spectra were recorded on a JEOL JMS-700 spectrometer by electrospray and chemical ionisation mass spectrometer operating at a resolution of 15,000 full widths at half height. Flash chromatography was performed using silica gel (Flourochem Scientific Silica Gel 60, 40–63 μ) as the stationary phase. TLC was performed on aluminium sheets pre-coated with silica (Merck Silica Gel 60 F_{254}). The plates were visualised by the quenching of UV fluorescence (λ_{max}254 nm) and/or by staining with either anisaldehyde, potassium permanganate, iodine or cerium ammonium molybdate followed by heating.

*3.1.1. 1-(Furan-2-yl)cyclopentanol, **20**.* Cyclopentanone **19** (1.90 g, 22.61 mmol) was added to a stirred suspension of magnesium sulfate (13.61 g, 113.05 mmol) in tetrahydrofuran (140 mL) under argon. The resulting mixture was then allowed to stir at room temperature for 2 h before being cooled to −78 °C. In a separate flask, furan (7.70 g, 113.05 mmol) was added to a −78 °C solution of *n*-BuLi (2.5 M in hexanes, 45 mL, 113.05 mmol) and TMEDA (13.14 g, 113.05 mmol) in tetrahydrofuran (100 mL) under argon. The resulting solution was stirred at −78 °C for 1 h, and was then transferred dropwise via cannula into the flask containing the cyclopentanone/magnesium sulfate mixture in tetrahydrofuran at −78 °C. The reaction was then allowed to warm to room temperature overnight before being quenched by the addition of ice water (100 mL) and extracted with Et_2O (3×75 mL). The combined organic layers were washed with satd aq $NaHCO_3$ (100 mL), dried over Na_2SO_4 and concentrated under vacuum. Purification of the crude residue by flash column chromatography (silica gel, 1:9 diethyl ether in petroleum ether) afforded 1-(furan-2-yl)cyclopentanol **20** (3.33 g, 97%) as a colourless oil.

^{1}H NMR (400 MHz; $CDCl_3$) δ_H: 7.32 (1H, dd, *J*=1.8, 0.8 Hz), 6.28 (1H, dd, *J*=3.2, 1.8 Hz), 6.18 (1H, dd, *J*=3.2, 0.8 Hz), 2.23 (1H, br s), 2.00–2.06 (2H, m), 1.88–1.95 (4H, m), 1.70–1.74 (2H, m); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C: 159.4, 141.5, 110.0, 104.1, 79.5, 39.6, 23.6; IR (thin film) ν_{max}=3342, 3323, 2966, 1695, 1504, 1450, 1396, 1001, 916, 804, 727, 680 cm^{-1}; HRMS (EI) observed M^+ 152.0834, calculated for $C_9H_{12}O_2$ 152.0837.

*3.1.2. 7-Hydroxy-6-oxaspiro[4.5]dec-8-en-10-one, **21**.* A 0 °C solution of 1-(furan-2-yl)cyclopentanol **20** (120 mg, 0.79 mmol) in chloroform (2 mL) under argon was treated with the portion-wise addition of *m*-chloroperbenzoic acid (77%, 267 mg, 1.2 mmol). The rate of addition was such that the temperature of the reaction was not allowed to exceed 10 °C throughout the process. Once the addition was completed, the reaction was stirred at 0 °C for 30 min, then for 1.5 h at room temperature. The reaction was quenched with satd aq $NaHCO_3$ (15 mL) and extracted with chloroform (3×10 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield 7-hydroxy-6-oxaspiro[4.5]dec-8-en-10-one **21** as a colourless oil, which was taken on to the next step without further purification.

*3.1.3. 7-Allyl-6-oxaspiro[4.5]dec-8-en-10-one, **22**.* A solution of the crude lactol **21** (96 mg, 0.6 mmol) in dichloromethane (9 mL) was treated with allyltrimethylsilane (197 mg, 274 μL, 1.8 mmol) under an argon atmosphere. The resulting mixture was cooled to −78 °C and boron trifluoride-diethyl etherate complex (82 mg, 70 μL, 0.6 mmol) was then added. The resulting reaction mixture was stirred at −78 °C until completion as indicated by TLC analysis (1 h). The reaction was then diluted with dichloromethane (15 mL) and quenched by the slow addition of aq satd ammonium chloride (25 mL). The phases were separated, and the aqueous layer was extracted with dichloromethane (3×15 mL). The combined organic layers were combined, washed with satd aq $NaHCO_3$ (25 mL), brine (25 mL), dried over Na_2SO_4, filtered and concentrated under vacuum. Purification of the crude residue by flash column chromatography (silica gel, 9:1 petroleum ether/diethyl ether) afforded the key 7-allyl-6-oxaspiro[4.5]dec-8-en-10-one **22** (36 mg, 54% over two steps) as a colourless oil.

^{1}H NMR (400 MHz; $CDCl_3$) δ_H: 6.85 (1H, ddd, *J*=10.4, 1.5, 0.4 Hz), 6.02 (1H, dd, *J*=10.3, 2.4 Hz), 5.83 (1H, ddt, *J*=17.3, 10.3, 6.8 Hz), 5.17–5.15 (1H, m), 5.14–5.09 (1H, m), 4.41 (1H, tt, *J*=6.7, 2.0 Hz), 2.49–2.40 (1H, m), 2.40–2.30 (1H, m), 2.14–2.06 (1H, m), 1.82–1.62 (5H, m), 1.53–1.44 (2H, m); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C: 23.3, 23.9, 31.8, 35.0, 38.2, 67.8, 88.3, 117.1, 125.1, 132.3, 148.7, 198.0; IR (thin film) ν_{max}=3080, 2956, 2923, 1727, 1685, 1643, 1466, 1449, 1275, 1180, 1073 cm^{-1}; HRMS (CI) observed $[M+H]^+$ 193.1228, calculated for $C_{12}H_{17}O_2$ 193.1229.

3.2. General procedure for the synthesis of alcohols 15, 23–25

Furan (1 equiv) was added to a stirred solution of *n*-butyllithium (2.5 M in hexanes, 1.0 equiv) and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (1 equiv) in tetrahydrofuran (10 mL) at −78 °C under argon. The solution was stirred at −78 °C under argon for 1 h before being treated with the cyclic ketone (0.2 equiv). The reaction mixture was then stirred at −78 °C for a further 1 h before being quenched with ice-cold satd aq ammonium chloride (15 mL) and extracted with diethyl ether (3×10 mL). The combined organics were dried over sodium sulfate, filtered and concentrated under vacuum.

*3.2.1. 1-(Furan-2-yl)cyclobutanol, **23**.* Furan (465 mg) was coupled with cyclobutanone (96 mg) using *n*-BuLi (2.7 mL) and TMEDA (794 mg) to afford after purification by flash column chromatography (silica gel, elution gradient 10%–20% diethyl ether in petroleum) 188 mg (quant.) of alcohol **23** as a colourless oil.

^{1}H NMR (400 MHz; $CDCl_3$) δ_H: 7.38 (1H, dd, *J*=1.7, 0.6 Hz), 6.33 (1H, dd, *J*=3.2, 1.8 Hz), 6.28 (1H, dd, *J*=3.2, 0.5 Hz), 2.55 (1H, br s), 2.53–2.46 (2H, m), 1.90–1.81 (2H, m), 1.70–1.58 (2H, m); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C: 12.1, 35.6, 72.2, 104.9, 110.0, 142.1, 158.1; IR (thin film) ν_{max}=3352, 2989, 2947, 1504, 1423, 1369, 1284, 1249, 1222, 1157, 1130, 1080, 1006, 956, 910, 883, 813, 729, 648 cm^{-1}; HRMS (CI) observed $[M-OH]^+$ 121.0650, calculated for C_8H_9O 121.0653.

*3.2.2. 1-(Furan-2-yl)cyclohexanol, **15**.* Furan (328 mg) was coupled with cyclohexanone (95 mg) using *n*-BuLi (1.9 mL) and TMEDA (561 mg) to afford after purification by flash column chromatography (silica gel, elution gradient 10%–20% diethyl ether in petroleum) 154 mg (96%) of alcohol **15** as a colourless oil.

^{1}H NMR (400 MHz; $CDCl_3$) δ_H: 7.34–7.32 (1H, m), 6.30 (1H, dd, *J*=3.2, 1.8 Hz), 6.19 (1H, d, *J*=3.2 Hz), 2.02–1.92 (3H, m), 1.87–1.78 (2H, m), 1.77–1.66 (2H, m), 1.57–1.26 (4H, m); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C: 22.2, 25.5, 36.5, 70.0, 104.4, 110.0, 141.3, 160.0; IR (thin film) ν_{max}=3407, 2935, 2859, 2360, 2337, 2248, 1501, 1448, 1342, 1259, 1224, 1155, 1057, 1038, 1008, 977, 958, 936, 905, 884, 726 cm^{-1}; HRMS (CI) observed $[M-OH]^+$ 149.0963, calculated for $C_{10}H_{13}O$ 149.0966.

*3.2.3. 1-(Furan-2-yl)cycloheptanol, **24**.* Furan (289 mg) was coupled with cycloheptanone (145 mg) using *n*-BuLi (1.7 mL) and TMEDA (493 mg) to afford after purification by flash column chromatography (silica gel, elution gradient 10%–20% diethyl ether in petroleum) 231 mg (99%) of alcohol **24** as a colourless oil.

^{1}H NMR (400 MHz; $CDCl_3$) δ_H: 7.35 (1H, appd, *J*=1.6 Hz), 6.30 (1H, dd, *J*=3.2, 1.8 Hz), 6.19 (1H, br d, *J*=3.2 Hz), 2.14 (2H, ddd, *J*=14.5, 9.6, 1.4 Hz), 1.97 (2H, ddd, *J*=14.4, 9.0, 1.2 Hz), 1.91 (1H, br s), 1.77–1.41 (8H, m); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C: 22.1, 29.4, 40.1, 74.1, 104.1, 109.9, 141.5, 160.8; IR (thin film) ν_{max}=3460, 2924, 2859, 2360, 2341, 1797, 1566, 1504, 1446, 1361, 1222, 1157, 1084, 1014, 883, 806, 732 cm^{-1}; HRMS (CI) observed $[M-OH]^+$ 163.1119, calculated for $C_{11}H_{15}O$ 163.1123.

*3.2.4. 1-(Furan-2-yl)cyclooctanol, **25**.* Furan (465 mg) was coupled with cyclooctanone (165 mg) using *n*-BuLi (2.6 mL) and TMEDA (761 mg) to afford after purification by flash column chromatography (silica gel, elution gradient 10%–16% diethyl ether in petroleum) 248 mg (98%) of alcohol **25** as a colourless oil.

^{1}H NMR (400 MHz; $CDCl_3$) δ_H: 7.35 (1H, dd, *J*=1.8, 0.7 Hz), 6.30 (1H, dd, *J*=3.2, 1.8 Hz), 6.20 (1H, dd, *J*=3.2, 0.7 Hz), 2.14–2.01 (4H, m), 1.88 (1H, br s), 1.75–1.59 (5H, m), 1.55–1.41 (5H, m); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C: 21.9, 24.6, 28.1, 34.8, 73.8, 104.8, 109.9, 141.5,

159.9; IR (thin film) ν_{max}=3398, 2924, 2854, 2360, 2341, 1790, 1504, 1465, 1446, 1361, 1319, 1219, 1157, 1118, 1087, 1018, 991, 925, 883, 848, 794, 732, 682, 667, 644 cm^{-1}; HMRS (CI) observed $[M-OH]^+$ 177.1274, calculated for $C_{12}H_{17}O$ 177.1279.

3.2.5. 6-Allyl-5-oxaspiro[3.5]non-7-en-9-one, 29 via 6-hydroxy-5-oxaspiro[3.5]non-7-en-9-one, ***26****.* Following the procedure for the synthesis of lactol **21**, a solution of 1-(furan-2-yl)cyclobutanol **23** (189 mg, 1.37 mmol) in chloroform (7 mL) was rearranged using *m*-CPBA (354 mg, 2.06 mmol) to afford lactol **26**, which was used without further purification.

Following the procedure for the synthesis of spiropyran **22**, a solution of 6-hydroxy-5-oxaspiro[3.5]non-7-en-9-one in anhydrous dichloromethane (3 mL) was treated with allyltrimethylsilane (469 mg, 4.10 mmol) and boron trifluoride-diethyl etherate (194 mg, 1.37 mmol). Purification by flash column chromatography (silica gel 9:1 hexane/diethyl ether) afforded 6-allyl-5-oxaspiro[3.5]non-7-en-9-one, **29** (24 mg, 10% over two steps) as a colourless oil.

^1H NMR (400 MHz; $CDCl_3$) δ_H: 6.85 (1H, dd, *J*=10.2, 1.5 Hz), 6.00 (1H, dd, *J*=10.3, 2.4 Hz), 5.86 (1H, ddt, *J*=17.2, 10.2, 7.1 Hz), 5.21–5.19 (1H, m), 5.18–5.14 (1H, m), 4.43 (1H, tt, *J*=6.6, 1.9 Hz), 2.74–2.65 (1H, m), 2.53–2.44 (1H, m), 2.40 (1H, dd, *J*=14.2, 7.1 Hz), 2.37–2.28 (1H, m), 2.13–2.01 (2H, m), 1.93–1.79 (2H, m); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C: 197.0, 149.6, 133.0, 125.1, 118.3, 80.8, 69.0, 39.0, 30.0, 29.9, 12.6; IR (thin film) ν_{max}=3078, 2953, 2848, 2362, 1745, 1687, 1642, 1462, 1446, 1417, 1385, 1337, 1308, 1254, 1206, 1186, 1161, 1093, 1072, 1023, 996, 959, 916, 861, 837, 801, 746, 693 cm^{-1}; HRMS (CI) observed $[M+H]^+$ 179.1067, calculated for $C_{11}H_{15}O_2$ 179.1072.

3.2.6. 2-Allyl-1-oxaspiro[5.5]undec-3-en-5-one 30 via 2-hydroxy-1-oxaspiro[5.5]un-7-en-9-one, ***17****.* Following the procedure for the synthesis of lactol **21**, a solution of 1-(furan-2-yl)cyclohexanol **15** (154 mg, 0.93 mmol) in chloroform (7 mL) was rearranged using *m*-CPBA (311 mg, 1.39 mmol) to afford lactol **17**, which was used without further purification.

Following the procedure for the synthesis of spiropyran **22**, a solution of 2-hydroxy-1-oxaspiro[5.5]un-7-en-9-one **17** in anhydrous dichloromethane (2 mL) was treated with allyltrimethylsilane (317 mg, 2.78 mmol) and boron trifluoride-diethyl etherate (131 mg, 0.93 mmol). Purification by flash column chromatography (silica gel 9:1 hexane/diethyl ether) afforded 2-allyl-1-oxaspiro[5.5]undec-3-en-5-one, **30** (120 mg, 63% over two steps) as a colourless oil.

^1H NMR (400 MHz; $CDCl_3$) δ_H: 6.84 (1H, dd, *J*=10.3, 1.4 Hz), 5.97 (1H, dd, *J*=10.3, 2.4 Hz), 5.91 (1H, dddd, *J*=17.0, 13.9, 7.4, 6.4 Hz), 5.22–5.10 (2H, m), 4.38 (1H, appt, *J*=6.7, 1.9 Hz), 2.52–2.35 (2H, m), 2.05–1.88 (2H, m), 1.72–1.44 (6H, m), 1.34–1.20 (2H, m); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C: 199.6, 149.5, 133.6, 125.3, 118.0, 79.1, 67.5, 39.3, 31.7, 28.4, 25.4, 21.5, 20.6; IR (thin film) ν_{max}=3076, 2930, 2855, 1796, 1771, 1683, 1642, 1462, 1450, 1443, 1434, 1386, 1360, 1336, 1285, 1264, 1244, 1205, 1160, 1150, 1084, 1064, 1041, 1027, 989, 944, 914, 853, 843, 834, 818, 801, 776, 727, 705, 693, 677 cm^{-1}; HRMS (CI) observed $[M+H]^+$ 207.1389, calculated for $C_{13}H_{19}O_2$ 207.1385.

3.2.7. 2-Allyl-1-oxaspiro[5.6]dodec-3-en-5-one 31 via 2-hydroxy-1-oxaspiro[5.6]dodec-3-en-5-one, ***27****.* Following the procedure for the synthesis of lactol **21**, a solution of 1-(furan-2-yl)cycloheptanol **24** (231 mg, 1.28 mmol) in chloroform (10 mL) was rearranged using *m*-CPBA (355 mg, 2.06 mmol) to afford lactol **27**, which was used without further purification.

Following the procedure for the synthesis of spiropyran **22**, a solution of 2-hydroxy-1-oxaspiro[5.6]dodec-3-en-5-one **27** in anhydrous dichloromethane (2 mL) was treated with allyltrimethylsilane (439 mg, 3.85 mmol) and boron trifluoride-diethyl etherate (182 mg, 1.28 mmol). Purification by flash column chromatography (silica gel 9:1 hexane/diethyl ether) afforded 2-allyl-1-oxaspiro[5.6]dodec-3-en-5-one, **31** (178 mg, 63% over two steps) as a colourless oil.

^1H NMR (400 MHz; $CDCl_3$) δ_H: 6.83 (1H, dd, *J*=10.3, 1.4 Hz), 5.94 (1H, dd, *J*=10.3, 2.4 Hz), 5.88 (1H, ddt, *J*=17.2, 10.2, 6.9 Hz), 5.20–5.10 (2H, m), 4.39 (1H, tt, *J*=6.9, 1.8 Hz), 2.51–2.42 (1H, m), 2.42–2.33 (1H, m), 2.19–2.10 (1H, m), 2.04–1.94 (1H, m), 1.74–1.48 (10H, m); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C: 200.2, 149.4, 133.5, 125.0, 118.0, 82.5, 67.8, 39.3, 36.4, 31.7, 29.3, 29.1, 22.1, 21.7; IR (thin film) ν_{max}=3078, 2924, 2857, 2702, 2358, 1723, 1683, 1642, 1460, 1444, 1436, 1388, 1335, 1300, 1278, 1247, 1211, 1201, 1164, 1148, 1064, 1037, 1017, 986, 957, 916, 859, 839, 797, 782, 753, 693 cm^{-1}; HRMS (CI) observed $[M+H]^+$ 221.1544, calculated for $C_{14}H_{21}O_2$ 221.1542.

3.2.8. 2-Allyl-1-oxaspiro[5.7]dodec-3-en-5-one, 32 via 2-hydroxy-1-oxaspiro[5.7]dodec-3-en-5-one, ***28****.* Following the procedure for the synthesis of lactol **21**, a solution of 1-(furan-2-yl)cyclooctanol **25** (248 mg, 1.28 mmol) in chloroform (10 mL) was rearranged using *m*-CPBA (429 mg, 1.92 mmol) to afford lactol **28**, which was used without further purification.

Following the procedure for the synthesis of spiropyran **22**, a solution of 2-hydroxy-1-oxaspiro[5.7]dodec-3-en-5-one **28** in anhydrous dichloromethane (3 mL) was treated with allyltrimethylsilane (438 mg, 3.83 mmol) and boron trifluoride-diethyl etherate (181 mg, 1.28 mmol). Purification by flash column chromatography (silica gel 9:1 hexane/diethyl ether) afforded 2-allyl-1-oxaspiro[5.7]dodec-3-en-5-one, **32** (182 mg, 61% over two steps) as a colourless oil.

^1H NMR (400 MHz; $CDCl_3$) δ_H: 6.82 (1H, dd, *J*=10.3, 1.4 Hz), 5.94 (1H, dd, *J*=10.3, 2.4 Hz), 5.88 (1H, dddd, *J*=17.0, 13.8, 7.3, 6.5 Hz), 5.19–5.11 (2H, m), 4.37 (1H, tt, *J*=6.6, 1.8 Hz), 2.50–2.42 (1H, m), 2.41–2.33 (1H, m), 2.16–2.09 (1H, m), 1.97–1.89 (1H, m), 1.82–1.45 (12H, m); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C: 200.1, 149.3, 133.5, 124.9, 117.9, 81.4, 67.8, 39.3, 32.2, 31.6, 28.5, 27.3, 22.6, 20.8, 20.7; IR (thin film) ν_{max}=3077, 2967, 2922, 2850, 2355, 1771, 1683, 1642, 1623, 1575, 1539, 1527, 1472, 1444, 1415, 1387, 1369, 1335, 1287, 1264, 1250, 1205, 1163, 1132, 1060, 1048, 1011, 992, 915, 861, 838, 797, 781, 767, 736, 727, 691 cm^{-1}; HRMS (CI) observed $[M+H]^+$ 235.1701, calculated for $C_{15}H_{23}O_2$ 235.1698.

3.2.9. 7-Allyl-6-oxaspiro[4.5]decan-10-one, ***33****.* A solution of 7-allyl-6-oxaspiro[4.5]dec-8-en-10-one **22** (488 mg, 2.6 mmol) in a deoxygenated benzene/water mixture (70 mL:141 μL) was transferred via cannula to a flask containing (triphenylphosphine) copper hydride hexamer (1.0 g, 0.51 mmol) under argon. The resultant red/brown suspension was stirred at room temperature overnight before being opened to the air, and being allowed to stir for 30 min. The suspension was filtered through Celite, concentrated under vacuum, and azeotroped with toluene to remove any residual benzene. Purification of the crude residue by flash column chromatography (silica gel, elution gradient 0%–5% ethyl acetate in hexanes) afforded 7-allyl-6-oxaspiro[4.5]decan-10-one **33** (476 mg, 84%) as a colourless oil.

^1H NMR (400 MHz; $CDCl_3$) δ_H: 5.73–5.55 (1H, m), 5.05–4.99 (2H, m), 3.79–3.71 (1H, m), 2.51 (1H, dm, *J*=16.1 Hz), 2.41 (1H, dm, *J*=16.1 Hz), 2.34–2.25 (1H, m), 2.22–2.13 (2H, m), 2.01–1.91 (2H, m), 1.88–1.76 (1H, m), 1.74–1.55 (6H, m); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C: 212.3, 134.6, 117.0, 91.6, 70.4, 40.2, 36.7, 36.0, 35.1, 30.5, 24.9, 24.4; IR (thin film) ν_{max}=3077, 2955, 2870, 2858, 2366, 1714, 1683, 1642, 1444, 1436, 1418, 1355, 1313, 1288, 1271, 1186, 1150, 1078, 1062, 1042, 1019, 995, 971, 914, 803, 754, 705, 640 cm^{-1}; HRMS (CI) observed $[M+H]^+$ 195.1387, calculated for $C_{12}H_{19}O_2$ 195.1385.

3.2.10. 7-Allyl-6-oxaspiro[4.5]decane, ***34****.* A room temperature solution of 7-allyl-6-oxaspiro[4.5]decan-10-one **33** (109 mg, 0.56 mmol)

in absolute ethanol (6 mL) under argon was treated with tosylhydrazide (110 mg, 0.59 mmol), and the resultant solution was stirred for 18.5 h. The reaction mixture was concentrated under vacuum and the residue was dissolved in anhydrous dichloromethane (5.4 mL) and cooled to 0 °C. Diisobutylaluminium hydride (1 M in hexanes, 2 mL, 2.0 mmol) was then added over 15 min and the resultant yellow solution was allowed to warm up to room temperature over1.5 h. The mixture was diluted with dichloromethane (10 mL), and quenched by the slow addition of 3 M NaOH soln (15 mL). The organic layer was separated and the aqueous phase was extracted with diethyl ether (3×10 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated under vacuum. Flash column chromatography of the crude residue (silica gel, petroleum ether) afforded 7-allyl-6-azaspiro[4.5]decane **34** (70.5 mg, 66%) as a colourless oil.

^{1}H NMR (400 MHz; $CDCl_3$) δ_H: 5.52 (1H, dddd, J=17.3, 10.2, 7.5, 6.4 Hz), 5.04 (1H, dm, J=17.2 Hz), 4.99 (1H, dm, J=10.3 Hz), 3.44 (1H, dtd, J=11.1, 6.5, 2.1 Hz), 2.24 (1H, dtt, J=14.2, 6.5, 1.5 Hz), 2.10 (1H, dm, J=14.1 Hz), 1.92–1.84 (1H, m), 1.76–1.62 (4H, m), 1.61–1.39 (9H, m); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C: 135.7, 116.1, 83.9, 71.4, 41.6, 41.4, 35.0, 32.7, 31.4, 24.4, 23.3, 21.4; IR (thin film) ν_{max}=3074, 2956, 2932, 2863, 2847, 2361, 1724, 1641, 1458, 1437, 1371, 1329, 1261, 1215, 1084, 1053, 1016, 997, 911, 863, 817, 803, 722 cm^{-1}; HRMS (CI) observed $[M+H]^+$ 181.1590, calculated for $C_{12}H_{21}O$ 181.1592.

3.2.11. (E)-Ethyl 2-methyl-4-(6-oxaspiro[4.5]decan-7-yl)but-2-enoate, ***35****.* A mixture of 7-allyl-6-oxaspiro[4.5]decane, **34** (100 mg, 0.56 mmol), Grubbs second generation catalyst (13.3 mg, 17 μmol) and ethyl methacrylate (1.4 mL, 11.2 mmol) was heated to reflux overnight. The reaction mixture was then concentrated under vacuum and the crude residue was purified by flash column chromatography (silica gel, elution gradient 0%–10% diethyl ether in petroleum ether) to yield (*E*)-ethyl 2-methyl-4-(6-azaspiro[4.5]decan-7-yl)but-2-enoate **35** (123 mg, 83%) as a colourless oil.

^{1}H NMR (400 MHz; $CDCl_3$) δ_H: 6.76 (1H, t, J=6.9 Hz), 4.25 (2H, q, J=6.9 Hz), 3.53–3.41 (1H, m), 2.34–2.18 (2H, m), 1.91–1.83 (1H, m), 1.80 (3H, br s), 1.26 (3H, t, J=6.9 Hz), 1.60–1.35 (9H, m), 1.75–1.62 (4H, m); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C: 168.2, 138.8, 128.9, 84.1, 70.8, 60.4, 41.5, 36.2, 34.8, 32.6, 31.6, 24.3, 23.2, 21.3, 14.3, 12.7; IR (thin film) ν_{max}=2955, 2931, 2867, 2848, 1708, 1650, 1457, 1439, 1387, 1366, 1329, 1280, 1252, 1233, 1217, 1173, 1143, 1110, 1095, 1082, 1055, 1018, 991, 869, 803, 745 cm^{-1}; HRMS (CI) observed $[M+H]^+$ 267.1957, calculated for $C_{16}H_{27}O_3$ requires 267.1960.

3.2.12. 2-(1-Azidocyclopentyl)furan, ***36****.* Lukewarm water (4.2 mL) was added to sodium azide (4.25 g, 65.44 mmol), and the resultant suspension was stirred for 15 min. Benzene (25 mL) was added, and the biphasic suspension was cooled to 0 °C. Concentrated H_2SO_4 (2.63 mL) was added dropwise, and the mixture was allowed to stir at 0 °C for 20 min. The organic phase was then carefully syringed into a dry flask at 0 °C, and 1-(furan-2-yl) cyclopentanol **20** (600 mg, 3.94 mmol) was added followed by H_2SO_4 (132 μL). The resulting mixture was stirred for 5 min at 0 °C and was then quenched with ice-cold ammonium hydroxide solution (25 mL). For safety reasons, 4 equiv batches of this procedure were performed simultaneously. The four quenched batches were combined, and extracted with EtOAc (3×20 mL). The combined organic phases were washed with satd aq NH_4Cl (25 mL), dried over Na_2SO_4 and concentrated under vacuum. Purification of the crude residue by flash column chromatography (silica gel, hexanes) afforded 2-(1-azidocyclopentyl)furan **36** (2.11 g, 76%) as a colourless oil.

^{1}H NMR (400 MHz; $CDCl_3$) δ_H: 7.39 (1H, dd, J=1.8, 0.8 Hz), 6.34 (1H, dd, J=3.2, 1.8 Hz), 6.28 (1H, dd, J=3.3, 0.7 Hz), 2.14–2.03 (4H, m), 1.93–1.73 (4H, m); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C: 155.4, 142.4, 110.1, 106.1, 70.5, 36.6, 23.3; IR (thin film) ν_{max}=2962, 2875, 2092, 1500, 1452, 1440, 1330, 1244, 1172, 1153, 1126, 1074, 1041, 1014, 968, 947, 906, 885, 846, 808, 734, 663 cm^{-1}; HRMS (EI) observed M^+ 177.0906, calculated for $C_9H_{11}N_3O$ 177.0902.

3.2.13. 1-(Furan-2-yl)cyclopentanamine, ***37****.* A solution of 2-(1-azidocyclopentyl)furan **36** (2.0 g, 11.29 mmol) in EtOAc (16 mL) was treated with 10% Pd/C (200 mg) and placed under a H_2 atmosphere. Hydrogen was bubbled through the solution for 5 min at 10 min intervals for a total of 1 h. The reaction mixture was then filtered through Celite and concentrated under vacuum to afford 1-(furan-2-yl)cyclopentanamine **37** (1.66 g, 97%) as a colourless oil, which was used without further purification.

^{1}H NMR (400 MHz; $CDCl_3$) δ_H: 7.31 (1H, dd, J=1.8, 0.8 Hz), 6.27 (1H, dd, J=3.2, 1.8 Hz), 6.08 (1H, dd, J=3.2, 0.7 Hz), 2.08–2.00 (2H, m), 1.92–1.83 (2H, m), 1.77–1.70 (6H, m); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C: 162.3, 141.1, 109.9, 102.8, 60.5, 40.1, 24.0; IR (thin film) ν_{max}=2956, 2924, 2870, 2854, 2360, 2330, 1728, 1458, 1377, 1261, 1074, 1014, 800, 738, 704, 699 cm^{-1}; HRMS (EI) observed M^+ 151.0991, $C_9H_{13}NO$ requires 151.0997.

3.2.14. N-(1-Furan-2-yl)cyclopentyl-4-toluenesulfonamide, ***38****.* A solution of 1-(furan-2-yl)cyclopentanamine **37** (1.66 g, 10.98 mmol) in anhydrous dichloromethane (25 mL) was treated with triethylamine (1.93 mL, 13.72 mmol) and cooled to 0 °C. The mixture was then treated with *p*-toluenesulfonyl chloride (2.62 g, 13.72 mmol), allowed to warm up to room temperature and stirred overnight. The reaction was then diluted with dichloromethane (20 mL) and washed sequentially with satd aq sodium hydrogen carbonate (25 mL) and brine (25 mL). The organic layer was separated, dried over sodium sulfate, filtered and concentrated under vacuum. Purification by flash column chromatography (silica gel, 20% ethyl acetate in hexanes) afforded *N*-(1-furan-2-yl)cyclopentyl-4-toluenesulfonamide **38** (2.29 g, 68%) as a white solid (mp 149 °C).

^{1}H NMR (400 MHz; $CDCl_3$) δ_H: 7.47 (2H, d, J=8.3 Hz), 7.10 (2H, d, J=8.3 Hz), 6.91 (1H, appdd, J=1.7, 0.7 Hz), 6.00 (1H, dd, J=3.3, 1.9 Hz), 5.98 (1H, dd, 3.1, 0.7 Hz), 5.18 (1H, br s), 2.35 (3H, s), 2.23–2.17 (2H, m), 2.10–2.03 (2H, m), 1.82–1.76 (2H, m), 1.62–1.58 (2H, m); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C: 155.0, 142.4, 141.6, 138.4, 129.2, 127.1, 109.7, 106.8, 64.2, 38.1, 22.4, 21.4; IR (thin film) ν_{max}=3254, 2972, 2953, 2918, 2875, 2364, 1915, 1599, 1496, 1460, 1427, 1315, 1290, 1251, 1222, 1153, 1096, 1004, 977, 950, 908, 860, 810, 752, 705, 669 cm^{-1}; HRMS (EI) observed M^+ 305.1085, calculated for $C_{16}H_{19}NO_3S$ 305.1086.

3.2.15. 7-Hydroxy-6-tosyl-6-azaspiro[4.5]dec-8-en-10-one, ***39****.* A 0 °C solution of *N*-(1-furan-2-yl)cyclopentyl-4-toluenesulfonamide, **38** (427 mg, 1.40 mmol) in chloroform (7 mL) was treated with the dropwise addition of *m*-chloroperbenzoic acid (≤77%, 470 mg, 2.10 mmol) at a rate such that the temperature did not exceed 10 °C during the addition. Once addition was completed, the reaction was allowed to warm to room temperature and stirred until completion as indicated by TLC analysis (3 h). The solution was diluted with chloroform (10 mL), washed with 20% aq KI (15 mL), 30% aq $Na_2S_2O_3$ (15 mL), $NaHCO_3$ (15 mL), water (15 mL) and brine (15 mL) sequentially. The organic phase was dried over Na_2SO_4, filtered and concentrated under vacuum to yield 7-hydroxy-6-tosyl-6-azaspiro[4.5]dec-8-en-10-one **39** as a yellow foam, which was taken forward without further purification.

3.2.16. 7-Allyl-6-tosyl-azaspiro[4.5]dec-8-en-10-one, ***40****.* A −78 °C solution of hemi-aminal **39**, (449 mg, 1.40 mmol) in anhydrous dichloromethane (7 mL) was treated with allyltrimethylsilane (319 mg, 2.79 mmol). Boron trifluoride-diethyl etherate (198 mg, 1.40 mmol) was then added and the resulting solution was stirred at −78 °C until completion by TLC analysis (45 min). The reaction mixture was diluted with dichloromethane (10 mL) and washed

with cold satd aq ammonium chloride (20 mL). The organic phase was dried over sodium sulfate, filtered and concentrated under vacuum. Purification of the crude residue by flash column chromatography (silica gel, elution gradient 10%–33% diethyl ether in petroleum ether) yielded 7-allyl-6-tosyl-azaspiro[4.5]dec-8-en-10-one, **40** (311 mg, 64% over two steps) as a white solid (mp 89–90 °C).

^{1}H NMR (400 MHz; $CDCl_3$) δ_H: 7.56 (2H, d, J=8.3 Hz), 7.21 (2H, d, J=8.3 Hz), 6.85 (1H, dd, J=4.6, 10.2 Hz), 6.00–5.91 (1H, m), 5.88 (1H, dd, J=10.2, 1.8 Hz), 5.22–5.20 (1H, m), 5.19–5.16 (1H, m), 5.11–5.04 (1H, m), 2.82 (1H, dtt, J=13.4, 6.4, 1.3 Hz), 2.60 (1H, dtm, J=13.4, 8.1 Hz), 2.37 (3H, s), 2.13–2.02 (3H, m), 1.80–1.71 (3H, m), 1.44–1.32 (2H, m); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C: 196.4, 146.2, 143.6, 139.0, 133.9, 129.8, 126.8, 124.8, 118.9, 73.1, 57.3, 42.5, 41.5, 32.2, 23.9, 22.6, 21.6; IR (thin film) ν_{max}=2957, 2874, 2360, 1681, 1598, 1575, 1495, 1432, 1416, 1377, 1341, 1329, 1307, 1264, 1166, 1089, 1067, 1000, 911, 846, 816, 794, 735, 702, 667, 647 cm^{-1}; HRMS (CI) observed $[M+H]^+$ 346.1476, calculated for $C_{19}H_{24}NO_3S$ 346.1477.

*3.2.17. 7-Allyl-6-azaspiro[4.5]decan-10-one, **41**.* A solution of 7-Allyl-6-azaspiro[4.5]dec-8-en-10-one **40** (300 mg, 1.89 mmol) in a deoxygenated benzene/water mixture (100 mL:0.2 mL) was transferred via cannula to a flask containing (triphenylphosphine) copper hydride hexamer (1.0 g, 0.51 mmol) under argon. The resultant red/brown suspension was stirred at room temperature overnight before being opened to the air, and being allowed to stir for 1 h. The suspension was filtered through Celite, concentrated under vacuum, and azeotroped with toluene to remove any residual benzene. Purification of the crude residue by flash column chromatography (silica gel, elution gradient 0%–10% ethyl acetate in hexanes) afforded 7-allyl-6-azaspiro[4.5]decan-10-one **41** (258 mg, 85%) as a white solid (mp 88–90 °C).

^{1}H NMR (400 MHz; $CDCl_3$) δ_H: 7.74 (2H, d, 8.3 Hz), 7.29 (2H, d, 8.1 Hz), 5.6–5.57 (1H, m), 5.06–5.04 (1H, m), 5.03–5.00 (1H, m), 4.05 (1H, ddt, J=10.7, 6.3, 4.6 Hz), 2.66 (1H, dt, J=15.7, 7.4 Hz), 2.50 (1H, ddd, J=16.9, 9.3, 6.8 Hz), 2.42 (3H, s), 2.41–2.30 (3H, m), 2.20–2.03 (3H, m), 1.98–1.88 (1H, m), 1.86–1.76 (3H, m), 1.74–1.64 (1H, m), 1.57–1.45 (1H, m); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C: 209.5, 143.4, 139.2, 134.2, 129.8, 127.2, 118.2, 76.5, 53.9, 39.4, 38.2, 36.6, 31.9, 25.5, 24.5, 24.1, 21.6; IR (thin film) ν_{max}=3070, 2955, 2877, 1712, 1643, 1597, 1442, 1411, 1311, 1234, 1149, 1095, 1003, 964, 902, 810, 763, 671 cm^{-1}; HRMS (CI) observed $[M+H]^+$ 348.1632, calculated for $C_{19}H_{26}NO_3S$ 348.1633.

*3.2.18. 7-Allyl-6-azaspiro[4.5]decane, **42**.* A room temperature solution of 7-allyl-6-azaspiro[4.5]decan-10-one, **41** (535 mg, 1.54 mmol) in absolute ethanol (15 mL) was treated with tosylhydrazide (315 mg, 1.69 mmol) and the resultant solution was allowed to stir at room temperature overnight. The solvent was evaporated under vacuum, and the crude tosylhydrazone was dissolved in dry dichloromethane (20 mL) and cooled down to 0 °C. Diisobutylaluminium hydride (5.4 mL, 1 M in hexanes) was then added dropwise to the solution over a period of 45 min. The reaction was then stirred at 0 °C until completion by TLC analysis (2 h). The reaction mixture was diluted with dichloromethane (20 mL), and quenched by the slow addition of 15% sodium hydroxide solution (15 mL). The mixture was diluted with water (10 mL), which resulted in the formation of a biphasic mixture, which was extracted with diethyl ether (3×15 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure. Purification of the crude residue by flash column chromatography (silica gel, 0%–15%–100% diethyl ether in petroleum ether) afforded 7-allyl-6-azaspiro[4.5]decane **42** (281 mg, 55%) as a yellow oil.

^{1}H NMR (400 MHz; $CDCl_3$) δ_H: 7.73 (1.2H, d, J=8.3 Hz), 7.65 (1.5H, d, 8.3 Hz), 7.24 (2H, d, J=8.2 Hz), 5.87–5.71 (1.4H, m), 5.12–5.05 (2H, m), 4.56–4.49 (0.4H, m), 4.32–4.22 (0.6H, m), 3.52–3.40 (1H, m), 2.66–2.50 (2H, m), 2.43–2.34 (1H, m), 2.40 (3H, s), 2.16–1.42 (14H, m); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C: 142.7, 142.5, 142.4, 141.7, 136.0, 129.7, 129.6, 129.5, 126.6, 126.4, 126.2, 125.8, 117.6, 117.5, 75.5, 69.2, 56.4, 55.1, 40.7, 40.0, 38.5, 36.5, 36.1, 33.8, 27.3, 26.1, 25.2, 25.1, 23.4, 23.2, 22.9, 21.6, 21.5, 20.3; IR (thin film) ν_{max}=3510, 3070, 2947, 2877, 1712, 1643, 1597, 1496, 1442, 1411, 1311, 1234, 1149, 1095, 1003, 964, 902, 810, 763, 702, 663, 601 cm^{-1}; HRMS (CI) observed $[M+H_2O-H]^+$ 350.1788, calculated for $C_{19}H_{28}NO_3S$ 348.1790.

*3.2.19. (E)-Ethyl 2-methyl-4-(6-azaspiro[4.5]decan-7-yl)but-2-enoate, **43**.* A solution of 7-allyl-6-azaspiro[4.5]decane, **42** (25 mg, 75 mmol) in neat ethyl methacrylate (187 μL, 1.50 mmol) was treated with Hoveyda–Grubbs second generation catalyst (5 mg, 8 mmol) and the resulting mixture was heated to reflux overnight. Upon completion by TLC analysis, the reaction mixture was concentrated under vacuum. Purification of the crude residue by flash column chromatography (silica gel, elution gradient 20%–50% ethyl acetate in hexanes) afforded (*E*)-ethyl 2-methyl-4-(6-azaspiro[4.5]decan-7-yl)but-2-enoate, **43** (15 mg, 48%) as a yellow oil.

^{1}H NMR (400 MHz; $CDCl_3$) δ_H: 7.73 (1H, d, J=8.2 Hz), 7.65 (1.5H, d, J=8.4 Hz), 7.25 (2H, d, J=8.1 Hz), 6.77 (0.4H, t, J=7.0 Hz), 6.70 (0.6H, t, J=6.8 Hz), 4.64–4.56 (0.4H, m), 4.37–4.29 (0.6H, m), 4.20 (0.8H, q, J=7.1 Hz), 4.18 (1.2H, q, J=7.0 Hz), 3.55–3.44 (1H, m), 2.88–2.59 (2H, m), 2.41 (3H, s), 2.43–2.34 (1.2H, m), 2.26–1.41 (14.8H, m), 1.29 (1.8H, t, J=7.1 Hz), 1.30 (1.2H, t, J=7.2 Hz); ^{13}C NMR (400 MHz; $CDCl_3$) δ_C: 168.1, 168.0, 142.9, 142.6, 142.4, 141.6, 138.5, 138.4, 130.1, 130.0, 129.8, 129.7, 126.4, 125.9, 75.2, 72.9, 71.7, 69.3, 60.8, 60.7, 56.3, 54.9, 38.8, 36.9, 36.4, 35.1, 34.5, 34.0, 27.3, 26.5, 25.9, 25.2, 23.7, 23.5, 23.1, 21.6, 21.5, 21.2, 14.4 (2C), 13.0, 12.9; IR (thin film) ν_{max}=3581, 2947, 2870, 2360, 2252, 1705, 1643, 1597, 1450, 1388, 1373, 1288, 1265, 1211, 1149, 1095, 1018, 972, 910, 810, 732, 663, 601 cm^{-1}; HRMS (FAB) observed $[M+H_2O-H]^+$ 436.2155, calculated for $C_{23}H_{34}NO_5S$ 436.2158.

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