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Synthesis of spirocyclic amines by using dipolar cycloadditions of nitrones

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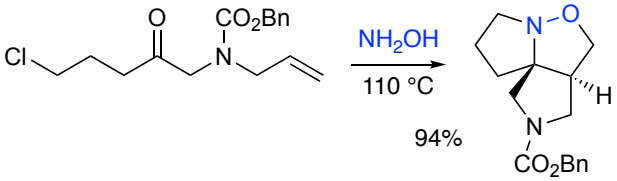
Aliphatic ketones containing a chloride and alkene were heated with hydroxylamine to promote cascade, tandem condensation to oximes, cyclization to nitrones and 1,3-dipolar cycloaddition to tricyclic isoxazolidines as single stereoisomers. Single regioisomers were obtained when three atoms linked the ketone and dipolarophile to give five-membered rings but mixtures resulted with four atoms in the tether unless a terminal ester was located on the alkene. The N–O bond in the products could be reduced to give spirocyclic amines and diamines.

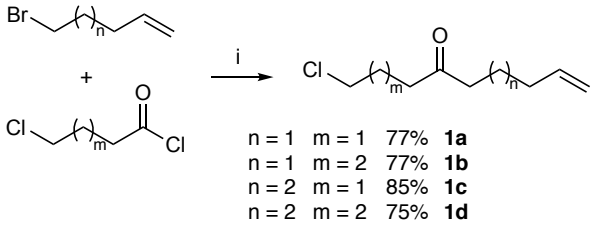


Over the last few years we have reported an efficient method to access polycyclic products by using a cascade process involving condensation of an aldehyde and an amine, cyclization of the resulting imine with displacement of a halide, and then dipolar cycloaddition.[1–5] This chemistry provides rapid access to fused or bridged cyclic amine products and has been applied to the preparation of natural products such as aspidospermidine,[1] quebrachamine,[1] myrioxazine A,[2] crispine A,[3] and macronecine.[4] An area that we wanted to explore was the use of ketones in place of aldehydes as this should allow access to spirocyclic amine products.[6]

Spirocyclic amines are present in several natural products, such as pinnaic acid and halichlorine,[7] and the lepadiformines and cylindricines.[8] Spirocycles are desirable scaffolds for drug discovery due to their 3D conformational structures and rigidity that reduces the loss of entropy upon ligand–protein binding.[9] The condensation of an *N*-alkylhydroxylamine and a cyclic ketone for the formation of a nitrone followed by dipolar cycloaddition is known to give spirocyclic isoxazolidines.[10,11] Alternatively, condensation of hydroxylamine with a ketone followed by in situ cyclization by conjugate addition gives a cyclic nitrone that can undergo cycloaddition to give spirocyclic products;[12,13] this chemistry has found use for the

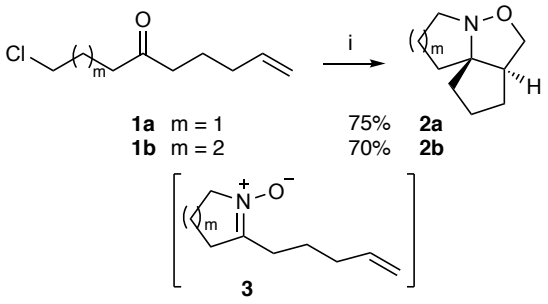
preparation of alkaloids such as histrionicotoxin.[14] Our methodology provides an alternative cyclization mode by displacement of a halide rather than conjugate addition.[15] This paper describes the simple preparation of functionalized ketones and their efficient cascade chemistry to give spirocyclic products.

We needed access to a variety of ketones to explore the effect on the cascade chemistry of the tether length between the carbonyl and the alkyl halide, and between the carbonyl and the alkene. These were prepared readily (~50% yield) by addition of Grignard reagents to acid chlorides,[16] however better yields of the ketones **1a**–**d** were obtained by addition of copper(I) bromide as a catalyst (Scheme 1).



Scheme 1 Preparation of ketones **1a–d**. i, Mg, THF, 72 °C, 3 h, then –78 °C, 10 mol% CuBr, then addition of the acid chloride and warm to room temp. over 17 h.

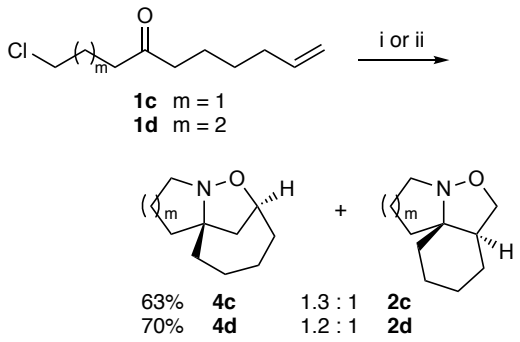
With ready access to the ketones **1a**–**d** in-hand, we set about testing the condensation, cyclization, and dipolar cycloaddition cascade chemistry. Heating the ketone **1a** with the hydrochloride salt of hydroxylamine and *N*,*N*-diisopropylethylamine in toluene gave the spirocyclic product **2a** in 75% yield as a single regio- and diastereoisomer (Scheme 2). Likewise, heating ketone **1b** with hydroxylamine gave the product **2b**. The reaction likely proceeds through condensation of the ketone and hydroxylamine, and displacement of chloride to give nitrone **3**, followed by dipolar cycloaddition to give the products **2a** and **2b**.[17]



Scheme 2 Cascade chemistry with the ketones **1a–b**. i, 1.5 equiv. $NH_2OH{\cdot}HCl$, $^{i}Pr_2NEt$, PhMe, 110 °C, 17 h, or with added 10 mol% *n*-Bu_4NI and 3.5 h to give **2b**, 89%.

Both ketones **1a** and **1b** reacted quickly with hydroxylamine, as judged by TLC analysis. An oxime intermediate could not be observed from ketone **1a**, indicating that cyclization with displacement of chloride is fast for 5-membered ring formation. However the cyclization was slower to give nitrone **3b** (m = 2). The efficiency of this process could be improved by addition of 10 mol% *n*-Bu_4NI. Cyclization on to the iodide should then be faster to give the 6-membered ring nitrone, and indeed in the presence of *n*-Bu_4NI as a catalyst the yield of the product **2b** increased to 89% with a reaction time of only 3.5 h. The oximes from these ketones should be formed as a mixture of *E* and *Z* isomers, yet only one of these (the *E*-isomer assigning the haloalkyl chain as a higher priority) can undergo ready cyclization to displace the halide. The high yields in the process indicate that the undesired *Z*-isomer can isomerise to the *E*-isomer.

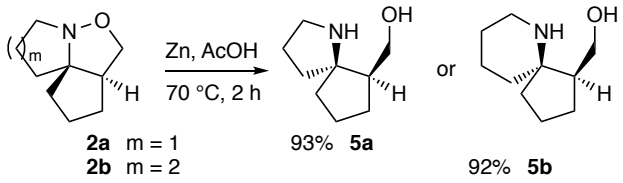
The cascade chemistry with ketones **1a** and **1b** provided a single regioisomer of the products **2a** and **2b** (Scheme 2). In contrast, the homologues **1c** and **1d**, with the extra methylene unit between the ketone and the alkene dipolarophile, gave a mixture of regiosiomeric products (Scheme 3).



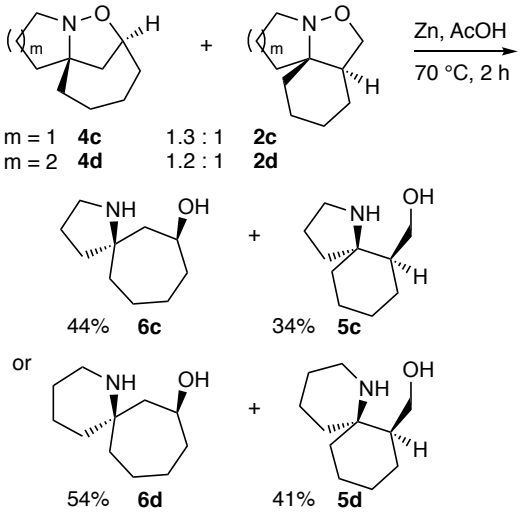
Scheme 3 Cascade chemistry with the ketones **1c–d**. i, for **1c**, 1.5 equiv. $NH_2OH{\cdot}HCl$, $^{i}Pr_2NEt$, xylene, 140 °C, 48 h; ii, for **1d**, 1.5 equiv. $NH_2OH{\cdot}HCl$, $^{i}Pr_2NEt$, 10 mol% *n*-Bu_4NI, xylene, 140 °C, 24 h.

We found that, in the absence of *n*-Bu_4NI, the ketone **1d** gave predominantly the oxime with only a small amount of the mixture of regioisomeric cycloaddition products. The regioisomeric cycloadducts were inseparable but each was a single stereoisomer as expected due to the constrained tricyclic ring structures.

The cycloadducts **2a**–**b** were heated with zinc and acetic acid to reduce the N–O bond to give the amino-alcohol products **5a** and **5b** (Scheme 4). Likewise, the mixture of **2c**+**4c** (and of **2d**+**4d**) gave the amino-alcohols **5c** and **6c** (and **5d** and **6d**) which were separable thereby providing single isomers of the desired products (Scheme 5). Single crystal X-ray analysis confirmed the structure and relative stereochemistry of the amino-alcohol **5d** (formed from the cycloadduct **2d**).



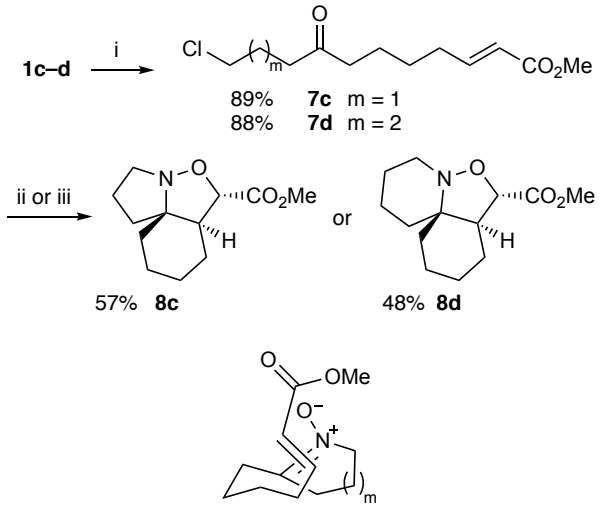
Scheme 4 Formation of amino-alcohols **5a**–**b**.



Scheme 5 Formation of amino-alcohols **5c–d** and **6c–d**.

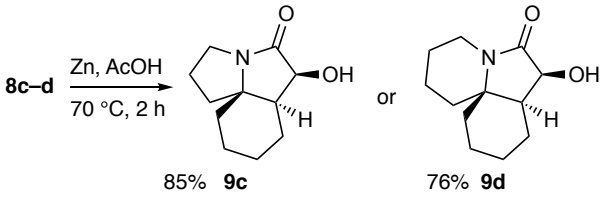
To influence the regiochemistry of the cycloaddition, we opted to install an electron-withdrawing group at the terminus of the alkene dipolarophile.[13,18] Cross metathesis with methyl acrylate gave the ketones **7c** and **7d** (Scheme 6). Subsequent treatment of these

ketones with hydroxylamine promoted nitrone formation and cycloaddition and we were pleased to find that a single regioisomer (and stereoisomer) was produced in each case. A possible arrangement for the cycloaddition, which explains the stereochemical outcome and matches that proposed in related work by Grigg and co-workers,[13] is shown in Scheme 6.



Scheme 6 Cascade chemistry with the ketones **7c–d**. i, methyl acrylate, 3 mol% GrubbsII, CH_2Cl_2, 42 °C, 22 h; ii, for **7c**, 2.2 equiv. $NH_2OH{\cdot}HCl$, $^{i}Pr_2NEt$, PhMe, 110 °C, 16 h; iii, for **7d**, 2.2 equiv. $NH_2OH{\cdot}HCl$, $^{i}Pr_2NEt$, 10 mol% *n*-Bu_4NI, PhMe, 110 °C, 16 h.

Treating the cycloadducts **8c** and **8d** with zinc and acetic acid reduced the N–O bond and promoted cyclization of the resulting secondary amine with the ester to give the lactam products **9c** and **9d** (Scheme 7). Single crystal X-ray analysis confirmed the structure and relative stereochemistry of the lactam **9d**.

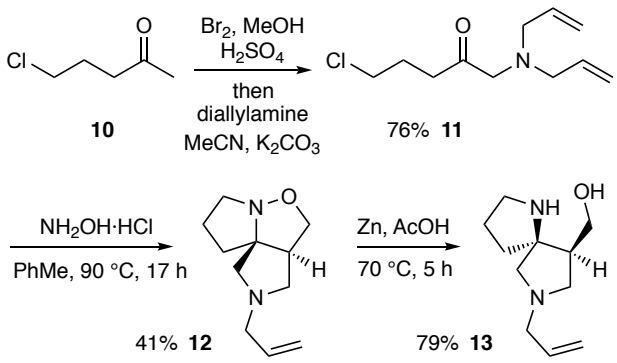


Scheme 7 Formation of lactams **9c–d**.

The methodology described above provides good yields of spirocyclic amines from acyclic ketones. To enhance the attractiveness of this approach from a medicinal chemistry perspective, we wanted to decrease the lipophilicity of the compounds and incorporate a

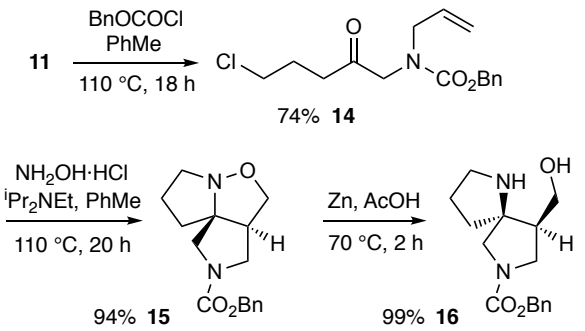
further handle for functionalization. This could be achieved by having a heteroatom in the chain in place of one of the methylene units.

Initially we chose the ketone **11** for these studies and this was prepared in two steps from the ketone **10** by regioselective bromination,[19] followed by reaction with diallylamine (Scheme 8). Heating the ketone **11** with the hydrochloride salt of hydroxylamine and *N*,*N*-diisopropylethylamine in toluene gave only a low yield (20%) of the tricyclic product **12** and it was apparent that the ketone **11** was unstable at high temperatures. The presence of an amino group within the molecule prompted us to explore the cascade chemistry in the absence of added *N*,*N*-diisopropylethylamine and we were pleased to find that this allowed the formation of the desired product **12** in improved yield (41%). The low yields are likely a result of the amino group in the chain reacting with the alkyl chloride. It was possible to reduce the N–O bond of the cycloadduct **12** to provide the amino-alcohol product **13**.



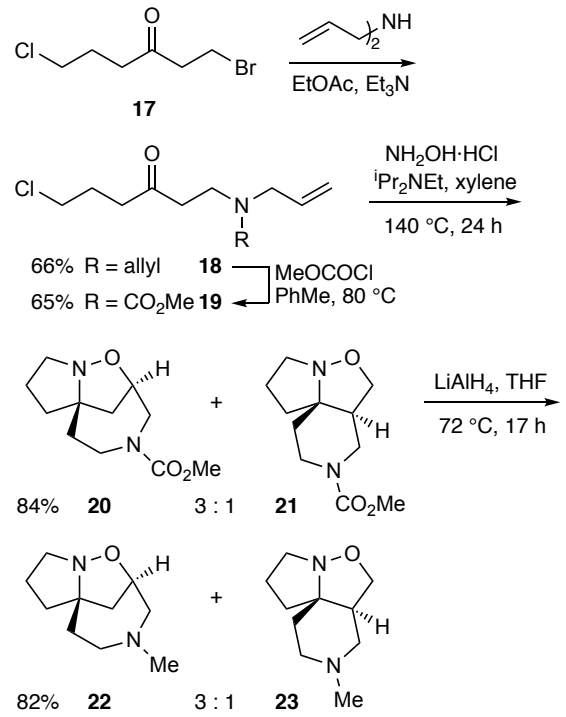
Scheme 8 Cascade chemistry with the ketone **11**.

To improve this chemistry, we treated the amine **11** with benzyl chloroformate to displace one of the allyl groups to give the carbamate **14** (Scheme 9). This substrate was better behaved in the cascade chemistry and led to the formation of tricyclic product **15** in high yield as a single isomer. This product was converted to the amino-alcohol **16** by reduction of the N–O bond.



Scheme 9 Cascade chemistry with the ketone **14**.

To further exemplify this chemistry, the ketone **19** was prepared, starting with the known bromide **17** (Scheme 10).[20] Addition of diallylamine gave the ketone **18** (which did not undergo the cascade chemistry and gave a complex mixture on heating with $NH_2OH{\cdot}HCl$). Conversion of the ketone **18** to the ketone **19** was carried out with methyl chloroformate.



Scheme 10 Cascade chemistry with the ketone **19**.

As expected based on our earlier work (Scheme 3), heating the ketone **19** with the hydrochloride salt of hydroxylamine and *N*,*N*-diisopropylethylamine gave a mixture of the regioisomeric products **20** and **21**. These were inseparable and the ratio of isomers was not

apparent from the NMR spectra due to the presence of rotamers. However, reduction with $LiAlH_4$ gave the amines **22** and **23** and allowed the deduction that the major isomer had the 7-membered ring (^{13}C NMR spectroscopy in $CDCl_3$ showed a CH at 79.1 ppm for the major isomer and a CH_2 at 70.0 ppm for the minor isomer, corresponding to the carbon attached to the oxygen atom).

Hence we have shown in this work that ketones are suitable substrates for a cascade of reactions involving condensation with hydroxylamine, cyclization with halide displacement to give a nitrone, and intramolecular dipolar cycloaddition to give tricyclic products. The N–O bond in the product can be reduced to give spirocyclic amines with a variety of ring sizes and substitution. The compounds prepared by this chemistry could find application as scaffolds for drug discovery.

EXPERIMENTAL SECTION

All reagents were obtained from commercial suppliers and were used without further purification unless otherwise specified. Petrol refers to petroleum ether (b.p. 40–60 °C). Reactions were carried out under nitrogen using oven-dried glassware. Thin layer chromatography was performed on silica plates and visualised by UV irradiation at 254 nm or by staining with an alkaline $KMnO_4$ dip. Column chromatography was performed using silica gel (40–63 micron mesh). ^1H NMR spectra chemical shifts are reported in ppm with respect to the residual solvent peaks, with multiplicities given as s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Coupling constants, *J*, are quoted to the nearest 0.5 Hz. High resolution (accurate mass) mass spectra (HRMS) used electrospray ionisation (ESI) with a time-of-flight (TOF) mass analyzer.

1-Chloronon-8-en-4-one **1a**. To a suspension of magnesium (0.11 g, 4.43 mmol) in THF (8 mL) at room temp., was added 5-bromo-1-pentene (0.50 mL, 4.22 mmol) slowly, and the mixture was heated to 72 °C. After 3 h, the mixture was allowed to cool to room temp. The mixture was cooled to –78 °C followed by adding copper bromide (0.06 g, 0.42 mmol). After 10 min, 4-chlorobutyryl chloride (0.50 mL, 4.22 mmol) was added and the mixture was

allowed to warm to room temp. over 17 h. The mixture was diluted with saturated aqueous ammonium chloride (5 mL) and was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and the solvent was evaporated. Purification by flash column chromatography, eluting with EtOAc–petrol (0.8:99.2 to 2:98), gave the ketone **1a** (0.57 g, 3.26 mmol, 77%) as an oil; ν_{max}/cm^{-1} 3075, 2935, 1715, 1640; R_f 0.6 [EtOAc–petrol (1:19)]; ^1H NMR (400 MHz, $CDCl_3$) δ = 5.84–5.74 (1H, m), 5.06–4.99 (2H, m), 3.60 (2H, t, *J* 7.0 Hz), 2.63 (2H, t, *J* 7.0 Hz), 2.46 (2H, t, *J* 7.0 Hz), 2.11–2.03 (4H, m), 1.72 (2H, quin, *J* 7.0 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 209.6, 137.9, 115.3, 44.5, 42.0, 39.3, 33.0, 26.3, 22.8; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_9H_{16}O^{35}Cl$ 175.0890; Found 175.0885; LRMS *m/z* (ES) 177 (30%, MH^+ for ^{37}Cl), 175 (100%, MH^+ for ^{35}Cl).

1-Chlorodec-9-en-5-one **1b**.[16] To a suspension of magnesium (0.11 g, 4.43 mmol) in THF (8 mL) at room temp., was added 5-bromo-1-pentene (0.50 mL, 4.22 mmol) slowly, and the mixture was heated to 72 °C. After 3 h, the mixture was allowed to cool to room temp. The mixture was cooled to –78 °C followed by adding copper bromide (0.06 g, 0.42 mmol). After 10 min, 5-chlorovaleroyl chloride (0.55 mL, 4.22 mmol) was added and the mixture was allowed to warm to room temp. over 17 h. The mixture was diluted with saturated aqueous ammonium chloride (5 mL) and was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and the solvent was evaporated. Purification by flash column chromatography, eluting with EtOAc–petrol (1:99 to 2:98), gave the ketone **1b** (0.61 g, 3.25 mmol, 77%) as an oil; ν_{max}/cm^{-1} 3080, 2935, 1710, 1645; R_f 0.6 [EtOAc–petrol (1:19)]; ^1H NMR (400 MHz, $CDCl_3$) δ = 5.84–5.73 (1H, m), 5.06–4.98 (2H, m), 3.55 (2H, t, *J* 7.0 Hz), 2.46 (2H, t, *J* 7.0 Hz), 2.43 (2H, t, *J* 7.0 Hz), 2.11–2.05 (2H, m), 1.83–1.67 (6H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 210.2, 137.9, 115.2, 44.6, 41.8, 41.7, 33.1, 31.9, 22.7, 21.0; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{10}H_{18}O^{35}Cl$ 189.1046; Found 189.1047; LRMS *m/z* (ES) 191 (30%, MH^+ for ^{37}Cl), 189 (100%, MH^+ for ^{35}Cl).

1-Chlorodec-9-en-4-one **1c**. To a suspension of magnesium (0.20 g, 8.23 mmol) in THF (16 mL) at room temp., was added 6-bromo-1-hexene (1.0 mL, 7.5 mmol) slowly, and the mixture was heated to 72 °C. After 3 h, the mixture was allowed to cool to room temp. The

mixture was cooled to –78 °C followed by adding copper bromide (0.11 g, 0.75 mmol). After 10 min, 4-chlorobutyryl chloride (0.85 mL, 7.5 mmol) was added and the mixture was allowed to warm to room temp. over 17 h. The mixture was diluted with saturated aqueous ammonium chloride (5 mL) and was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and the solvent was evaporated. Purification by flash column chromatography, eluting with EtOAc–petrol (0.5:99.5 to 2:98), gave the ketone **1c** (1.20 g, 6.36 mmol, 85%) as an oil; ν_{max}/cm^{-1} 3080, 2930, 1715, 1640; R_f 0.6 [EtOAc–petrol (1:19)]; ^1H NMR (400 MHz, $CDCl_3$) δ = 5.83–5.76 (1H, m), 5.06–4.96 (2H, m), 4.30 (2H, t, *J* 7.0 Hz), 2.63 (2H, t, *J* 7.0 Hz), 2.45 (2H, t, *J* 7.0 Hz), 2.11–2.03 (4H, m), 1.66–1.60 (2H, m), 1.45–1.37 (2H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 209.8, 138.4, 114.7, 44.5, 42.8, 39.2, 33.5, 28.4, 26.3, 23.3; HRMS (ESI-TOF) *m/z*: $[M]^+$ Calcd for $C_{10}H_{17}O^{35}Cl$ 188.0962; Found 188.0968; LRMS *m/z* (ES) 190 (30%, M^+ for ^{37}Cl), 188 (100%, M^+ for ^{35}Cl).

1-Chloroundec-10-en-5one **1d**.[16] To a suspension of magnesium (0.19 g, 7.85 mmol) in THF (15 mL) at room temp., was added 6-bromo-1-hexene (1.0 mL, 7.5 mmol) slowly, and the mixture was heated to 72 °C. After 3 h, the mixture was allowed to cool to room temp. The mixture was cooled to –78 °C followed by adding copper bromide (0.11 g, 0.75 mmol). After 10 min, 5-chlorovaleroyl chloride (1.0 mL, 7.5 mmol) was added and the mixture was allowed to warm to room temp. over 17 h. The mixture was diluted with saturated aqueous ammonium chloride (5 mL) and was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and the solvent was evaporated. Purification by flash column chromatography, eluting with EtOAc–petrol (0.5:99.5 to 2:98), gave the ketone **1b** (1.14 g, 5.62 mmol, 75%) as an oil; ν_{max}/cm^{-1} 3075, 2940, 1715, 1640; R_f 0.6 [EtOAc–petrol (1:19)]; ^1H NMR (400 MHz, $CDCl_3$) δ = 5.86–5.76 (1H, m), 5.05–4.96 (2H, m), 3.56 (2H, t, *J* 7.0 Hz), 2.46 (2H, t, *J* 7.0 Hz), 2.43 (2H, t, *J* 7.0 Hz), 2.11–2.05 (2H, m), 1.83–1.70 (4H, m), 1.65–1.50 (2H, m), 1.44–1.37 (2H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 210.4, 138.4, 114.6, 44.6, 42.6, 41.7, 33.5, 31.9, 28.4, 23.2, 21.0; HRMS (ESI-TOF) *m/z*: $[M]^+$ Calcd for $C_{11}H_{19}O^{35}Cl$ 202.1119; Found 202.1120; LRMS *m/z* (ES) 204 (30%, M^+ for ^{37}Cl), 202 (100%, M^+ for ^{35}Cl).

(1RS,8RS)-6-Oxa-5-azatricyclo[6.3.0.0^{1,5}]undecane **2a**. To ketone **1a** (219 mg, 1.25 mmol) in toluene (15 mL) was added hydroxylamine hydrochloride (104 mg, 1.5 mmol) and diisopropylethylamine (0.55 mL, 3.0 mmol) and the mixture was heated to 110 °C. After 17 h, the mixture was allowed to cool to room temp. and the solvent was evaporated. Purification by flash column chromatography, eluting with MeOH–CH_2Cl_2 (1:99 to 2:98), gave the cycloadduct **2a** (144 mg, 0.94 mmol, 75%) as an oil; ν_{max}/cm^{-1} 2945, 2865, 1440; R_f 0.5 [MeOH–CH_2Cl_2 (5:95)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.08 (1H, br t, *J* 8.5 Hz), 3.41 (1H, dd, *J* 8.5, 6.5 Hz), 3.33–3.27 (1H, m) 3.00–2.93 (1H, m), 2.66–2.61 (1H, m), 2.04–1.96 (2H, m), 1.92–1.87 (1H, m), 1.84–1.65 (5H, m), 1.60–1.56 (1H, m), 1.53–1.45 (1H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 83.5, 72.3, 56.2, 56.0, 39.8, 37.9, 31.2, 25.4, 24.9; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_9H_{16}NO$ 154.1232; Found 154.1232; LRMS *m/z* (ES) 154 (100%, MH^+).

(1RS,5RS)-7-Oxa-8-azatricyclo[6.4.0.0^{1,5}]dodecane **2b**.[17] To ketone **1b** (265 mg, 1.41 mmol) in toluene (15 mL) was added hydroxylamine hydrochloride (118 mg, 1.69 mmol) and diisopropylethylamine (0.60 mL, 3.38 mmol, 3.0 equiv) and the mixture was heated to 110 °C. After 17 h, the mixture was allowed to cool to room temp. and the solvent was evaporated. Purification by flash column chromatography, eluting with MeOH–CH_2Cl_2 (1:99 to 2:98), gave the cycloadduct **2b** (166 mg, 0.99 mmol, 70%) as an oil.

Alternatively,

To ketone **1b** (362 mg, 1.92 mmol) in toluene (20 mL) was added hydroxylamine hydrochloride (200 mg, 2.88 mmol), diisopropylethylamine (1.0 mL, 5.76 mmol) and tetra-*n*-butylammonium iodide (71 mg, 0.19 mmol) and the mixture was heated to 110 °C. After 2 h, the mixture was allowed to cool to room temp. and the solvent was evaporated. Purification by flash column chromatography, eluting with MeOH–CH_2Cl_2 (1:99 to 2:98), gave the cycloadduct **2b** (286 mg, 1.71 mmol, 89%) as an oil; R_f 0.5 [MeOH–CH_2Cl_2 (5:95)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.31 (1H, br t, *J* 8.5 Hz) 3.48 (1H, dd, *J* 8.5, 5.0 Hz), 3.05–3.14 (1H, br m), 2.91–2.86 (1H, m), 2.66–2.61 (1H, m), 1.97–1.60 (8H, m), 1.56–1.41 (4H, m); ^{13}C

NMR (101 MHz, $CDCl_3$) δ = 75.2, 72.2, 50.4, 50.0, 39.2, 33.1, 31.3, 24.1, 22.9, 21.5. Data consistent with that in the literature.[17]

(1RS,8RS)-6-Oxa-5-azatricyclo[6.4.0.0^{1,5}]dodecane **2c** *and (1RS,7RS)-6-Oxa-5-azatricyclo[5.4.1.0^{1,5}]dodecane* **4c**. To ketone **1c** (396 mg, 2.10 mmol) in xylene (21 mL) was added hydroxylamine hydrochloride (219 mg, 3.15 mmol) and diisopropylethylamine (1.10 mL, 6.30 mmol) and the mixture was heated to 140 °C. After 48 h, the mixture was allowed to cool to room temp. and the solvent was evaporated. Purification by flash column chromatography, eluting with MeOH–CH_2Cl_2 (1:99 to 2:98), gave the cycloadducts **2c** and **4c** (220 mg, 1.32 mmol, 63%) as an inseparable mixture (1:1.3) as an oil; ν_{max}/cm^{-1} 2915, 2850, 1445; R_f 0.5 [MeOH–CH_2Cl_2 (5:95)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.39–4.35 (0.57H, m), 3.71 (0.43H, dd, *J* 7.0, 5.5 Hz), 3.42 (0.43H, dd, *J* 7.0, 3.0 Hz), 3.34 (0.43H, ddd, *J* 12.0, 7.0, 3.0 Hz), 3.11–2.98 (1.14H, m), 2.88–2.81 (0.43H, m), 2.03–1.91 (1.14H, m), 1.87–1.75 (1.14H, m), 1.74–1.50 (4.29H, m), 1.48–1.02 (7H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 78.6, 73.2, 72.9, 72.5, 57.5, 56.9, 48.5, 41.0, 40.1, 38.5, 36.6, 34.5, 34.3, 27.2, 24.2, 24.1, 23.5, 23.3, 22.6, 21.7; HRMS (ESI-TOF) *m/z*: $[M]^+$ Calcd for $C_{10}H_{17}NO$ 167.1305; Found 167.1313; LRMS *m/z* (ES) 167 (100%, M^+).

(1RS,9RS)-7-Oxa-6-azatricyclo[7.4.0.0^{1,6}]tridecane **2d** *and (1RS,8RS)-7-Oxa-6-azatricyclo[6.4.1.0^{1,6}]tridecane* **4d**. To ketone **1d** (751 mg, 3.71 mmol) in toluene (37 mL) was added hydroxylamine hydrochloride (387 mg, 5.57 mmol), diisopropylethylamine (2.0 mL, 11.1 mmol) and tetra-*n*-butylammonium iodide (137 mg, 0.37 mmol) and the mixture was heated to 140 °C. After 24 h, the mixture was allowed to cool to room temp. and the solvent was evaporated. Purification by flash column chromatography, eluting with MeOH–CH_2Cl_2 (0.5:99.5 to 2:98), gave the cycloadducts **2d** and **4d** (474 mg, 2.62 mmol, 71%) as an inseparable mixture (1:1.2) as an oil; ν_{max}/cm^{-1} 2940, 2850, 1445; R_f 0.5 [MeOH–CH_2Cl_2 (5:95)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.74 (0.55H, br d, *J* 8.0 Hz), 4.27 (0.45H, dd, *J* 10.0, 7.5 Hz), 3.76 (0.45H, br t, *J* 8.0 Hz), 3.21–3.17 (0.55H, m), 3.14–3.09 (0.45H, m), 2.85–2.76 (0.9H, m), 2.63–2.57 (0.55H, m), 2.55–2.49 (0.55H, m), 2.19–2.15 (0.45H, m), 2.03–1.59 (8H, m), 1.58–1.26 (6.1H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 77.4, 69.1, 65.3, 63.0, 53.0,

50.2, 45.8, 38.8, 35.6, 33.8, 33.7, 31.2, 30.7, 24.7, 24.6, 24.4, 23.5, 23.2, 22.0, 20.9, 19.8, 19.6; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{11}H_{20}NO$ 182.1539; Found 182.1537; LRMS *m/z* (ES) 182 (100%, MH^+).

(5RS,6RS)-1-Azaspiro[4.4]nonan-6-ylmethanol **5a**. Zinc powder (462 mg, 7.06 mmol) was added to cycloadduct **2a** (256 mg, 1.68 mmol) in AcOH/H_2O (9 mL, 1:2), and the mixture was heated to 70 °C. After 2 h, before being allowed to cool to room temp., the zinc salts were filtered, washing the filtrate with CH_2Cl_2 (20 mL), and the solvent was evaporated. The residue was partitioned between aqueous ammonia (18 M, 10 mL) and CH_2Cl_2 (20 mL) and was separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and the solvent was evaporated to give the alcohol **5a** (244 mg, 1.57 mmol, 93%) as an oil; ν_{max}/cm^{-1} 3295, 2950, 1440; R_f 0.3 [MeOH–CH_2Cl_2 (5:95)]; ^1H NMR (400 MHz, $CDCl_3$) δ = 3.68–3.63 (2H, m), 3.05–3.00 (1H, m), 2.91–2.85 (1H, m), 1.89–1.82 (1H, m), 1.78–1.56 (9H, m), 1.53–1.48 (1H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 72.5, 64.4, 47.0, 46.3, 39.3, 38.7, 26.3, 26.1, 21.9; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_9H_{18}NO$ 156.1383; Found 156.1381; LRMS *m/z* (ES) 156 (100%, MH^+).

(1RS,5RS)-6-Azaspiro[4.5]decan-1-ylmethanol **5b**.[17a] Zinc powder (275 mg, 4.2 mmol) was added to cycloadduct **2b** (167 mg, 1 mmol) in AcOH/H_2O (5 mL, 1:2), and the mixture was heated to 70 °C. After 2 h, before being allowed to cool to room temp., the zinc salts were filtered, washing the filtrate with CH_2Cl_2 (20 mL), and the solvent was evaporated. The residue was partitioned between aqueous ammonia (18 M, 8 mL) and CH_2Cl_2 (20 mL) and was separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and the solvent was evaporated to give the amino alcohol **5b** (155 mg, 0.92 mmol, 92%) as an amorphous solid; m.p. 82–84 °C, lit.[17a] m.p. for **5b** 84 °C; R_f 0.3 [MeOH–CH_2Cl_2 (5:95)]; ^1H NMR (400 MHz, $CDCl_3$) δ = 3.88 (1H, dd, *J* 11.5, 4.0 Hz), 3.64 (1H, dd, *J* 11.5, 6.5 Hz), 2.91–2.87 (1H, m), 2.77 (1H, dt, *J* 11.5, 3.0 Hz), 1.87–1.66 (7H, m), 1.64–1.38 (6H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 63.7, 63.5, 49.6, 42.2, 37.1, 35.6, 26.9, 26.3, 22.4, 22.3. Data consistent with that in the literature.[17a]

(5S,6S)-1-Azaspiro[4.5]decan-6-ylmethanol **5c** *and (5RS,7RS)-1-Azaspiro[4.6]undecan-7-ol* **6c**. Zinc powder (319 mg, 4.87 mmol) was added to the 1:1.3 mixture of cycloadducts **2c** and **4c** (195 mg, 1.16 mmol) in AcOH/H_2O (6 mL, 1:2), and the mixture was heated to 70 °C. After 2 h, before being allowed to cool to room temp., the zinc salts were filtered, washing the filtrate with CH_2Cl_2 (20 mL), and the solvent was evaporated. The residue was partitioned between aqueous ammonia (18 M, 10 mL) and CH_2Cl_2 (20 mL) and was separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and the solvent was evaporated. Purification by flash column chromatography, eluting with conc. NH_3–MeOH–CH_2Cl_2 (1:9:90), gave the alcohol **5c** (68 mg, 0.40 mmol, 34%) as an oil and the alcohol **6c** (86 mg, 0.51 mmol, 44%) as an oil.

Data for alcohol **5c** ν_{max}/cm^{-1} 3280, 2920, 1450; R_f 0.5 [conc. NH_3–MeOH–CH_2Cl_2 (1:9:90)]; ^1H NMR (400 MHz, $CDCl_3$) δ = 3.89–3.80 (2H, m), 2.99–2.93 (2H, m), 1.99–1.95 (2H, m), 1.83–1.66 (3H, m), 1.63–1.52 (7H, m), 1.40–1.28 (3H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 65.2, 65.0, 45.2, 43.1, 37.3, 36.0, 27.0, 25.7, 23.9, 23.4; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{10}H_{20}NO$ 170.1539; Found 170.1540; LRMS *m/z* (ES) 170 (100%, MH^+).

Data for alcohol **6c** ν_{max}/cm^{-1} 3380, 2930, 1450; R_f 0.2 [conc. NH_3–MeOH–CH_2Cl_2 (1:9:90)]; ^1H NMR (400 MHz, $CDCl_3$) δ = 4.11–4.06 (1H, m), 3.10–2.97 (4H, m), 2.03 (1H, dd, *J* 14.5, 6.5 Hz), 1.91–1.73 (7H, m), 1.70–1.50 (6H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 69.5, 65.9, 45.6, 44.1, 41.2, 41.0, 37.3, 25.0, 24.3, 24.2; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{10}H_{20}NO$ 170.1539; Found 170.1540; LRMS *m/z* (ES) 170 (100%, MH^+).

(6RS,7RS)-1-Azaspiro[5.5]undecan-7-ylmethanol **5d** *and (6RS,8RS)-1-Azaspiro[5.6]dodecan-8-ol* **6d**. Zinc powder (453 mg, 6.93 mmol) was added to the 1:1.2 mixture of cycloadducts **2d** and **4d** (299 mg, 1.65 mmol) in AcOH/H_2O (9 mL, 1:2), and the mixture was heated to 70 °C. After 2 h, before being allowed to cool to room temp., the zinc salts were filtered, washing the filtrate with CH_2Cl_2 (20 mL), and the solvent was evaporated. The residue was partitioned between aqueous ammonia (18 M, 10 mL) and CH_2Cl_2 (20 mL) and was separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and the solvent was evaporated.

Purification by flash column chromatography, eluting with conc. NH_3–MeOH–CH_2Cl_2 (1:9:90), gave the alcohol **5d** (125 mg, 0.68 mmol, 41%) as an amorphous solid and the alcohol **6d** (164 mg, 0.89 mmol, 54%) as an amorphous solid.

Data for alcohol **5d** m.p. 56–58 °C; ν_{max}/cm^{-1} 3275, 2920, 1435; R_f 0.6 [conc. NH_3–MeOH–CH_2Cl_2 (1:9:90)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.33 (1H, dd, *J* 11.0, 3.0 Hz), 3.47 (1H, dd, *J* 11.0, 3.0 Hz), 2.83–2.71 (2H, m), 2.38–2.34 (1H, m), 2.14–2.06 (1H, m), 1.84–1.74 (2H, m), 1.64–1.46 (6H, m), 1.35–1.24 (4H, m), 0.90–0.83 (1H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 65.3, 54.8, 44.9, 39.9, 34.2, 29.8, 25.9, 25.3, 25.2, 20.9, 19.7; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{11}H_{22}NO$ 184.1701; Found 184.1701; LRMS *m/z* (ES) 184 (100%, MH^+). For X-ray data, see SI and CCDC 1537946.

Data for alcohol **6d** m.p. 70–73 °C; ν_{max}/cm^{-1} 3250, 2920, 1450; R_f 0.2 [conc. NH_3–MeOH–CH_2Cl_2 (1:9:90)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.11 (1H, br t, *J* 11.0 Hz), 2.91–2.74 (2H, m), 2.34 (2H, br s), 2.08 (1H, dd, *J* 14.5, 8.0 Hz), 1.93–1.85 (1H, m), 1.83–1.69 (4H, m), 1.68–1.57 (5H, m), 1.51–1.27 (5H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 69.1, 54.5, 43.8, 40.5, 39.4, 38.0, 37.8, 26.3, 25.8, 22.1, 20.1; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{11}H_{22}NO$ 184.1701; Found 184.1699; LRMS *m/z* (ES) 184 (100%, MH^+).

Methyl (2E)-11-Chloro-8-oxoundec-2-enoate **7c**. To ketone **1c** (648 mg, 3.43 mmol) in degassed CH_2Cl_2 (120 mL) was added methyl acrylate (0.70 mL, 6.86 mmol). The mixture was heated to 45 °C before Grubbs' 2nd generation catalyst (71 mg, 0.10 mmol) in CH_2Cl_2 (20 mL) was added slowly. After 22 h, the reaction mixture was opened up to air and was allowed to cool to room temp. then the solvent was evaporated. Purification by flash column chromatography, eluting with EtOAc–petrol (1:19 to 1:4), gave the ketone **7c** (750 mg, 3.04 mmol, 89%) as an oil; ν_{max}/cm^{-1} 3005, 2930, 1715, 1640; R_f 0.3 [EtOAc–petrol (1:4)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.97 (1H, dt, *J* 15.5, 7.0 Hz), 5.87 (1H, dt, *J* 15.5, 1.5 Hz), 3.75 (3H, s), 3.60 (2H, t, *J* 7.0 Hz), 2.62 (2H, t, *J* 7.0 Hz), 2.46 (2H, t, *J* 7.0 Hz), 2.27 (2H, qd, *J* 7.0, 1.5 Hz), 2.10 (2H, quin, *J* 7.0 Hz), 1.67 (2H, quin, *J* 7.0 Hz), 1.51 (2H, quin, *J* 7.0 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 209.4, 167.0, 148.9, 121.2, 51.4, 44.5, 42.5, 39.2, 31.9,

27.5, 26.2, 23.1; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{12}H_{19}O_3{}^{35}ClNa$ 269.0920; Found 269.0909; LRMS *m/z* (ES) 271 (30%, MNa^+ for ^{37}Cl), 269 (100%, MNa^+ for ^{35}Cl).

Methyl (2E)-12-Chloro-8-oxododec-2-enoate **7d**. To ketone **1d** (495 mg, 2.44 mmol) in degassed CH_2Cl_2 (90 mL) was added methyl acrylate (0.45 mL, 4.88 mmol). The mixture was heated to 45 °C before Grubbs' 2nd generation catalyst (62 mg, 0.07 mmol) in CH_2Cl_2 (15 mL) was added slowly. After 22 h, the reaction mixture was opened up to air and was allowed to cool to room temp. then the solvent was evaporated. Purification by flash column chromatography, eluting with EtOAc–petrol (1:19 to 1:4), gave the ketone **7d** (561 mg, 2.15 mmol, 88%) as an oil; ν_{max}/cm^{-1} 3055, 2990, 1715, 1660; R_f 0.3 [EtOAc–petrol (1:4)]; ^1H NMR (400 MHz, $CDCl_3$) δ = 6.97 (1H, dt, *J* 15.5, 7.0 Hz), 5.86 (1H, dt, *J* 15.5, 1.5 Hz), 3.75 (3H, s), 3.56 (2H, t, *J* 6.5 Hz), 2.48–2.42 (4H, m), 2.24 (2H, qd, *J* 7.0, 1.5 Hz), 1.83–1.72 (4H, m), 1.66–1.60 (2H, m), 1.51–1.44 (2H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 210.0, 167.0, 148.9, 121.2, 51.4, 44.6, 42.3, 41.7, 2 × 31.9, 27.5, 23.1, 21.0; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{13}H_{21}O_3{}^{35}ClNa$ 283.1077; Found 283.1067; LRMS *m/z* (ES) 285 (30%, MNa^+ for ^{37}Cl), 283 (100%, MNa^+ for ^{35}Cl).

Methyl (1RS,7RS,8RS)-6-Oxa-5-azatricyclo[6.4.0.0^{1,5}]dodecane-7-carboxylate **8c**. To ketone **7c** (109 mg, 0.44 mmol) in toluene (5 mL) was added hydroxylamine hydrochloride (67 mg, 0.97 mmol) and diisopropylethylamine (0.18 mL, 1.06 mmol) and the mixture was heated to 110 °C. After 16 h, the reaction mixture was allowed to cool to room temp. and the solvent was evaporated. Purification by flash column chromatography, eluting with MeOH–CH_2Cl_2 (0.5:99.5 to 1:99), gave the cycloadduct **8c** (57 mg, 0.25 mmol, 57%) as an oil; ν_{max}/cm^{-1} 2950, 1730, 1435; R_f 0.6 [MeOH–CH_2Cl_2 (5:95)]; ^1H NMR (400 MHz, $CDCl_3$) δ = 4.44 (1H, d, *J* 9.5 Hz), 3.79 (3H, s), 3.35–3.31 (2H, m), 2.61–2.57 (1H, m), 2.07–1.81 (4H, m), 1.77–1.42 (7H, m), 1.33–1.22 (1H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 172.9, 81.4, 72.6, 54.7, 52.3, 50.0, 33.8, 32.9, 23.9, 22.9, 21.4, 21.1; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{12}H_{20}NO_3$ 226.1438; Found 226.1441; LRMS *m/z* (ES) 226 (100%, MH^+).

Methyl (1RS,8RS,9RS)-7-Oxa-6-azatricyclo[7.4.0.0^{1,6}]tridecane-8-carboxylate **8d**. To ketone **7d** (414 mg, 1.59 mmol) in toluene (16 mL) was added hydroxylamine hydrochloride (243

mg, 3.5 mmol), diisopropylethylamine (0.66 mL, 3.8 mmol) and tetra-*n*-butylammonium iodide (60 mg, 0.16 mmol) and the mixture was heated to 110 °C. After 16 h, the reaction mixture was allowed to cool to room temp. and the solvent was evaporated. Purification by flash column chromatography, eluting with MeOH–CH_2Cl_2 (0.5:99.5 to 1:99), gave the cycloadduct **8d** (184 mg, 0.77 mmol, 48%) as an oil; ν_{max}/cm^{-1} 2935, 1750, 1450; R_f 0.6 [MeOH–CH_2Cl_2 (5:95)]; ^1H NMR (400 MHz, $CDCl_3$) δ = 4.45 (1H, d, *J* 9.5 Hz), 3.80 (3H, s), 3.30–3.28 (1H, m), 3.00–2.94 (1H, m), 2.90–2.88 (1H, m), 2.24–2.20 (1H, m), 1.98–1.93 (1H, m), 1.87–1.79 (1H, m), 1.75–1.72 (1H, m), 1.67–1.29 (10H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 173.9, 79.2, 64.3, 52.3, 52.1, 44.4, 35.5, 30.6, 24.8, 22.7, 21.7, 20.5, 19.5; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{13}H_{22}NO_3$ 240.1594; Found 240.1598; LRMS *m/z* (ES) 240 (100%, MH^+).

(5RS,10aRS,10bRS)-5-Hydroxy-octahydro-1H-cyclohexa[h]pyrrolizin-6-one **9c**. Zinc powder (286 mg, 4.37 mmol) was added to cycloadduct **8c** (234 mg, 1.04 mmol) in AcOH/H_2O (5 mL, 1:2), and the mixture was heated to 70 °C. After 2 h, before being allowed to cool to room temp., the zinc salts were filtered, washing the filtrate with CH_2Cl_2 (20 mL), and the solvent was evaporated. The residue was partitioned between aqueous ammonia (18 M, 10 mL) and CH_2Cl_2 (20 mL) and was separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and the solvent was evaporated. The crude solid was left to stand at rt for 17 h then purification by flash column chromatography, eluting with MeOH–CH_2Cl_2 (5:95), give the alcohol **9c** (172 mg, 0.88 mmol, 85%) as an amorphous solid; m.p. 170–172 °C; ν_{max}/cm^{-1} 3245, 2920, 1665; R_f 0.4 [MeOH–CH_2Cl_2 (5:95)]; ^1H NMR (400 MHz, $CDCl_3$) δ = 5.31 (1H, d, *J* 4.5 Hz), 4.37 (1H, dd, *J* 6.5, 4.5 Hz), 3.56–3.49 (1H, m), 3.22–3.16 (1H, m), 2.28–2.08 (2H, m), 2.05–1.93 (3H, m), 1.82–1.52 (6H, m), 1.41–1.34 (1H, m), 1.26–1.13 (1H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 174.4, 79.4, 69.8, 45.3, 40.1, 35.2, 34.8, 25.8, 23.3, 23.2, 22.4; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{11}H_{18}NO_2$ 196.1332; Found 196.1334; LRMS *m/z* (ES) 196 (100%, MH^+).

(7RS,7aRS,11aRS)-7-Hydroxy-decahydropyrido[2,1-r269234]indol-6-one **9d**. Zinc powder (409 mg, 6.26 mmol) was added to cycloadduct **8d** (356 mg, 1.49 mmol) in AcOH/H_2O (10

mL, 1:2), and the mixture was heated to 70 °C. After 2 h, before being allowed to cool to room temp., the zinc salts were filtered, washing the filtrate with CH_2Cl_2 (20 mL), and the solvent was evaporated. The residue was partitioned between aqueous ammonia (18 M, 10 mL) and CH_2Cl_2 (20 mL) and was separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and the solvent was evaporated to give the alcohol **9d** (237 mg, 1.13 mmol, 76%) as an amorphous solid; m.p. 163–165 °C; ν_{max}/cm^{-1} 3300, 2910, 1660; R_f 0.4 [MeOH–CH_2Cl_2 (5:95)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.31 (1H, dd, *J* 7.5, 2.5 Hz), 3.99 (1H, dd, *J* 13.0, 4.5 Hz), 2.84 (1H, dt, *J* 13.0, 3.0 Hz), 2.74 (1H, d, *J* 2.5 Hz), 2.01–1.90 (3H, m), 1.77–1.67 (7H, m), 1.56–1.44 (2H, m), 1.40–1.22 (3H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 174.1, 73.1, 59.8, 44.2, 37.0, 34.0, 30.2, 24.7, 23.4, 22.0, 21.3, 19.7; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{12}H_{20}NO_2$ 210.1489; Found 210.1490; LRMS *m/z* (ES) 210 (100%, MH^+). For X-ray data, see SI and CCDC 1537947.

5-Chloro-1-[di(prop-2-en-1-yl)amino]pentan-2-one **11**. To 5-chloro-2-pentanone **10** (2.0 mL, 16.5 mmol) in methanol (20 mL) was added bromine (0.80 mL, 16 mmol) slowly at –10 °C. The mixture was stirred at –10 °C for 1 h, then at room temp. for 1 h. Water (10 mL) and sulphuric acid (18 M, 10 mL) were added and the mixture was stirred at room temp. for 17 h. The mixture was diluted with water (20 mL) and was extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with 10% aqueous solution $NaHCO_3$ (30 mL), water (30 mL), then dried ($MgSO_4$), filtered, and the solvent was evaporated to give 1-bromo-5-chloro-2-pentanone (3.61 g, 18.1 mmol) as an oil (used without further purification). To this bromide (3.61 g, 18.1 mmol) in acetonitrile (60 mL) was added diallylamine (2.25 mL, 18.1 mmol) and potassium carbonate (3.75 g, 27.1 mmol) at room temp. After 17 h, the reaction mixture was diluted with 10% aqueous $NaHCO_3$ (15 mL) and water (15 mL) and was extracted with EtOAc (3 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered, and the solvent was evaporated. Purification by flash column chromatography, eluting with EtOAc–petrol (1:9 to 1:4), gave the ketone **11** (2.98 g, 13.8 mmol, 76%) as an oil; ν_{max}/cm^{-1} 2815, 1715, 1645; R_f 0.4 [EtOAc–petrol (2:8)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ =

5.88–5.76 (2H, m), 5.19–5.13 (4H, m), 3.55 (2H, t, *J* 6.5 Hz), 3.24 (2H, s), 3.13 (4H, d, *J* 6.5 Hz), 2.62 (2H, t, *J* 6.5 Hz), 2.02 (2H, quin, *J* 6.5 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 209.4, 135.0, 118.4, 62.6, 57.8, 44.5, 36.9, 26.2; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{11}H_{19}NO^{35}Cl$ 216.1155; Found 216.1165; LRMS *m/z* (ES) 218 (35%, MH^+ for ^{37}Cl), 216 (100%, MH^+ for ^{35}Cl).

(1RS, 5RS)-3-(Prop-2-en-1-yl)-7-oxa-3,8-diazatricyclo[6.3.0.0^{1,5}]undecane **12**. To aminoketone **11** (590 mg, 2.74 mmol) in toluene (30 mL) was added hydroxylamine hydrochloride (285 mg, 4.11 mmol) and the mixture was heated at 90 °C for 18 h. Following this, water (10 mL) and NaOH (1 M, 10 mL) were added. The mixture was extracted with CH_2Cl_2 (4 × 15 mL), dried ($MgSO_4$) and the solvent was evaporated. Purification by flash column chromatography, eluting with NH_3–MeOH–CH_2Cl_2 (1:2:97), gave cycloadduct **12** (220 mg, 41%) as an oil; ν_{max}/cm^{-1} 3080, 2955, 2785, 1135, 1025; R_f 0.37 [NH_3–MeOH–CH_2Cl_2 (1:2:97)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.96–5.86 (1H, m), 5.20–5.05 (2H, m), 4.04 (1H, t, *J* 8 Hz), 3.60 (1H, dd, *J* 8 and 6 Hz), 3.27–3.21 (1H, m), 3.15–3.10 (1H, m), 3.03–2.98 (1H, m), 2.97–2.92 (1H, m), 2.87–2.85 (1H, m), 2.69–2.61 (m, 2H), 2.51–2.47 (m, 1H), 2.32–2.29 (1H, m), 2.05–1.90 (2H, m), 1.80–1.67 (2H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 135.8, 116.8, 81.8, 71.3, 65.4, 58.5, 58.0, 56.1, 55.7, 36.4, 24.4; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{11}H_{18}N_2O$ 195.1492; Found 195.1496; LRMS *m/z* (ES) 195 (100%, MH^+).

[(5RS, 9RS)-7-(Prop-2-en-1-yl)-1,7-diazaspiro[4.4]nonan-9-yl]methanol **13**. To a solution of cycloadduct **12** (280 mg, 1.44 mmol) in AcOH/H_2O (1:2, 15 mL) was added Zn dust (396 mg, 6.05 mmol) and the mixture was heated at 70 °C for 5 h. Before being allowed to cool, the zinc salts were removed by filtration, washing with CH_2Cl_2 and the solvent was evaporated. The residue was partitioned between aqueous ammonia solution (18 M, 5 mL) and CH_2Cl_2 (10 mL), the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL) and the solvent was evaporated to give the alcohol **13** (223 mg, 1.14 mmol, 79%) as an oil; ν_{max}/cm^{-1} 3300, 2955, 1645; R_f 0.39 [NH_3-MeOH-CH_2Cl_2 (1:9:90)]; ^{1}H NMR (400 MHz, $CDCl_3$) 5.91–5.80 (1H, m), 5.19–5.06 (2H, m), 3.94–3.44 (4H, m), 3.14–3.04 (2H, m), 3.02–2.87 (2H, m) 2.71–2.67

(1H, m), 2.58–2.50 (2H, m), 2.43–2.41 (1H, m), 2.10–2.03 (1H, m), 1.88–1.64 (4H, m); ^{13}C NMR (101 MHz, $CDCl_3$) 135.6, 116.9, 70.3, 67.0, 62.6, 59.1, 55.2, 47.0, 45.9, 38.0, 25.4; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{11}H_{21}N_2O$ 197.1654; Found 197.1649; LRMS *m/z* (ES) 197 (100%, MH^+).

Benzyl (5-Chloro-2-oxopentyl)prop-2-en-1-ylcarbamate **14**. To ketone **11** (2.39 g, 11.1 mmol) in toluene (50 mL) was added benzyl chloroformate (4.75 mL, 33.3 mmol) and the mixture was heated to 110 °C. After 17 h, the reaction mixture was allowed to cool to room temp. and the solvent was evaporated. Purification by flash column chromatography, eluting with EtOAc–petrol (1:9 to 1:4), gave the ketone **14** (2.53 g, 8.17 mmol, 74%) as an oil; ν_{max}/cm^{-1} 3024, 2955, 1735, 1695; R_f 0.4 [EtOAc–petrol (1:4)]; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ = 7.37–7.28 (5H, m), 5.84–5.75 (1H, m), 5.19–5.11 (4H, m), 4.06 (1H, s), 4.01–3.96 (3H, m), 3.57 (1H, t, *J* 6.5 Hz), 3.46 (1H, t, *J* 6.5 Hz), 2.62 (1H, t, *J* 6.5 Hz), 2.48 (1H, t, *J* 6.5 Hz), 2.07 (1H, quin, *J* 6.5 Hz), 1.95 (1H, quin, *J* 6.5 Hz); ^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ = 205.0, 156.3 & 155.8, 136.5 & 136.3, 133.3 & 133.2, 128.5, 128.1 & 128.0, 127.7, 118.1 & 117.5, 67.6, 55.7 & 55.2, 51.2 & 50.7, 44.3 & 44.1, 36.4 & 36.2, 26.1 & 26.0; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{21}NO_3{}^{35}Cl$ 310.1204; Found 310.1208; LRMS *m/z* (ESI) 312 (35%, MH^+ for ^{37}Cl), 310 (100%, MH^+ for ^{35}Cl).

Benzyl (1RS,8SR)-6-Oxa-5-azatricyclo[6.3.0.0^{1,5}]undecane-10-carboxylate **15**. To ketone **14** (1.10 g, 3.54 mmol) in toluene (40 mL) was added hydroxylamine hydrochloride (369 mg, 5.31 mmol) and diisopropylethylamine (1.85 mL, 10.62 mmol) and the mixture was heated to 110 °C. After 17 h, the reaction mixture was allowed to cool to room temp. and the solvent was evaporated. Purification by flash column chromatography, eluting with MeOH–CH_2Cl_2 (0.5:99.5 to 1.5:98.5), gave the cycloadduct **15** (957 mg, 3.32 mmol, 94%) as an oil; ν_{max}/cm^{-1} 3030, 2970, 1690; R_f 0.5 [MeOH–CH_2Cl_2 (5:95)]; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ = 7.38–7.32 (5H, m), 5.19–5.07 (2H, m), 4.16–4.12 (1H, m), 3.91 (1H, d, *J* 11.5 Hz), 3.66–3.56 (1H, m), 3.76–3.61 (2H, m), 3.39–3.26 (2H, m), 3.09–3.07 (1H, br m), 2.87–2.86 (1H, m), 2.08–1.95 (2H, m), 1.91–1.81 (2H, m); ^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ = 154.6 & 154.4, 136.7 & 136.6, 128.5 & 128.4, 128.0 & 127.95, 127.9 & 127.8, 82.3 & 81.3, 71.4,

66.9, 56.5, 54.8 & 54.1, 50.0, 35.3 & 35.1, 25.0; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{21}N_2O_3$ 289.1547; Found 289.1546; LRMS *m/z* (ESI) 289 (100%, MH^+).

Benzyl (5RS,9RS)-9-(Hydroxymethyl)-1,7-diazaspiro[4.4]nonane-7-carboxylate **16**. Zinc powder (909 mg, 13.9 mmol) was added to cycloadduct **15** (957 mg, 3.32 mmol) in AcOH/H_2O (20 mL, 1:2), and the mixture was heated to 70 °C. After 2 h, before being allowed to cool to room temp., the zinc salts were filtered, washing the filtrate with CH_2Cl_2 (40 mL), and the solvent was evaporated. The residue was partitioned between aqueous ammonia (18 M, 20 mL) and CH_2Cl_2 (40 mL) and was separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 40 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and the solvent was evaporated to give the alcohol **16** (958 mg, 3.30 mmol, 99%) as an oil; ν_{max}/cm^{-1} 3395, 3010, 2955, 1675; R_f 0.3 [MeOH–CH_2Cl_2 (5:95)]; ^1H NMR (500 MHz, $CDCl_3$, rotamers) δ = 7.35–7.30 (5H, m), 5.11 (2H, s), 3.83 (1H, dt, J 12.0, 2.5 Hz), 3.75–3.37 (6H, m), 3.29 (1H, dd, *J* 11.0, 4.5 Hz), 2.97–2.92 (2H, m), 2.03–1.99 (1H, m), 1.88–1.73 (4H, m); ^{13}C NMR (126 MHz, $CDCl_3$, rotamers) δ = 155.1 & 154.9, 136.7, 128.4, 128.1 & 128.0, 127.8, 70.2 & 69.5, 66.9, 61.2 & 60.8, 57.8 & 57.2, 47.4 & 46.9, 46.1, 45.9 & 45.3, 35.4 & 34.6, 25.9; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{23}N_2O_3$ 291.1703; Found 291.1702; LRMS *m/z* (ESI) 291 (100%, MH^+).

1-Bromo-6-chlorohexan-3-one **17**.[20b] To ethyl 4-chlorobutyrate (1.00 mL, 7.14 mmol) in Et_2O (25 mL) was added titanium(IV) isopropoxide (0.25 mL, 0.86 mmol) and EtMgBr (6.1 mL, 15.7 mmol, 2.6 M) at room temp. After 17 h, the reaction mixture was diluted with saturated aqueous ammonium chloride (15 mL) and was extracted with Et_2O (3 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered, and the solvent was evaporated to give an intermediate cyclopropanol (1.21 g, 9.02 mmol) as an oil (used without further purification). To this cyclopropanol (1.21 g, 9.02 mmol) and potassium carbonate (1.50 g, 10.8 mmol) in CH_2Cl_2 (30 mL) was added bromine (0.51 mL, 9.9 mmol) slowly at 0 °C. After 1 h, the mixture was diluted with saturated aqueous sodium thiosulfate (10 mL) and water (10 mL) and was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with saturated aqueous sodium thiosulfate (30 mL), water (30 mL), then dried ($MgSO_4$),

filtered, and the solvent was evaporated to give the crude product ketone **17** (1.39 g, 6.52 mmol, 91%) which was used without further purification; R_f 0.4 [EtOAc–petrol (1:9)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.63–3.58 (4H, m), 3.06 (2H, t, *J* 6.5 Hz), 2.68 (2H, t, *J* 7.0 Hz), 2.10 (2H, quin, *J* 6.5 Hz). Data consistent with that in the literature.[20b]

6-Chloro-1-[di(prop-2-en-1-yl)amino]hexan-3-one **18**. To ketone **17** (1.68 g, 7.87 mmol) in EtOAc (40 mL) was added diallylamine (1.0 mL, 7.87 mmol) and triethylamine (1.10 mL, 7.87 mmol) at room temp. After 17 h, the reaction mixture was diluted with 10% aqueous $NaHCO_3$ (15 mL) and water (15 mL) and was extracted with EtOAc (3 × 40 mL). The combined organic layers were dried ($MgSO_4$), filtered, and the solvent was evaporated. Purification by flash column chromatography, eluting with EtOAc–petrol (1:9 to 1:4), gave the ketone **18** (1.19 g, 5.18 mmol, 66%) as an oil; ν_{max}/cm^{-1} 2815, 1715, 1645; R_f 0.4 [EtOAc–petrol (2:8)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.90–5.80 (2H, m), 5.23–5.17 (4H, m), 3.59 (2H, t, *J* 6.5 Hz), 3.12 (4H, br d, *J* 6.5 Hz), 2.80 (2H, t, *J* 7.0 Hz), 2.67–2.60 (4H, m), 2.07 (2H, quin, *J* 6.5 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 208.9, 135.0, 117.9 , 56.8, 47.9, 44.5, 40.7, 39.5, 26.2; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{12}H_{21}NO^{35}Cl$ 230.1306; Found 230.1301; LRMS *m/z* (ES) 232 (30%, MH^+ for ^{37}Cl), 230 (100%, MH^+ for ^{35}Cl).

Methyl (6-Chloro-3-oxohexyl)prop-2-en-1-ylcarbamate **19**. To ketone **18** (368 mg, 1.6 mmol) in toluene (16 mL) was added methyl chloroformate (0.45 mL, 5.6 mmol) and the mixture was heated to 80 °C. After 17 h, the reaction mixture was allowed to cool to room temp. and the solvent was evaporated. Purification by flash column chromatography, eluting with EtOAc–petrol (1:9 to 1:4), gave the carbamate **19** (257 mg, 1.04 mmol, 65%) as an oil; ν_{max}/cm^{-1} 3085, 2960, 1705, 1650; R_f 0.4 [EtOAc–petrol (1:4)]; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ = 5.78 (1H, br m), 5.21–5.17 (2H, m), 3.94–3.86 (2H, m), 3.72 (3H, br s), 3.60 (2H, t, *J* 6.5 Hz), 3.51–3.49 (2H, m), 2.77–2.71 (2H, m), 2.64 (2H, t, *J* 6.5 Hz), 2.06 (2H, quin, *J* 6.5 Hz); ^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ = 208.3 &208.0, 156.6, 133.7, 117.2 & 116.6, 52.7, 50.3, 44.4, 42.5 & 41.9, 41.5 & 41.0, 39.6, 26.1; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{11}H_{19}NO_3{}^{35}Cl$ 248.1048; Found 248.1048; LRMS *m/z* (ESI) 250 (35%, MH^+ for ^{37}Cl), 248 (100%, MH^+ for ^{35}Cl).

Methyl (1RS,7RS)-6-Oxa-5,9-diazatricyclo[5.4.1.0^{1,5}]dodecane-9-carboxylate **20** *and Methyl (1RS,8SR)-6-Oxa-5,10-diazatricyclo[6.4.0.0^{1,5}]dodecane-10-carboxylate* **21**. To ketone **19** (136 mg, 0.55 mmol) in xylene (6 mL) was added hydroxylamine hydrochloride (58 mg, 0.83 mmol) and diisopropylethylamine (0.30 mL, 1.65 mmol) and the mixture was heated to 140 °C. After 17 h, the reaction mixture was allowed to cool to room temp. and the solvent was evaporated. Purification by flash column chromatography, eluting with MeOH–CH_2Cl_2 (1:99 to 2:98), gave the cycloadducts **20** and **21** (103 mg, 0.46 mmol, 84%, (3:1)) as an oil; ν_{max}/cm^{-1} 2980, 1690; R_f 0.5 [MeOH–CH_2Cl_2 (5:95)]; ^{1}H NMR (400 MHz, C_6D_6, rotamers) δ = 4.29 (0.45H, q, *J* 4.0 Hz), 4.22–4.19 (0.3H, m), 4.17–4.12 (0.45H, ddd, *J* 14.5, 4.0, 1.0 Hz), 4.10–4.06 (0.3H, m), 3.71–3.67 (0.45H, m), 3.58–3.54 (0.45H, m), 3.50 (0.75H, s), 3.49 (1.35H, s), 3.45 (0.9H, s), 3.44–3.30 (1.5H, m), 3.20–3.14 (1.05H, m), 2.97 (0.75H, dd, *J* 14.5, 7.5 Hz), 2.68–2.57 (1.05H, m), 1.87–1.80 (0.45H, m), 1.68–1.54 (2.25H, m), 1.47–1.18 (5.25H, m), 1.06–0.99 (0.3H, m); ^{13}C NMR (101 MHz, C_6D_6, rotamers) δ = 156.4, 155.8, 78.7 & 78.4, 71.5, 71.2, 68.7, 56.7 & 56.6, 55.9, 52.0, 51.9, 51.6 & 51.5, 49.0, 43.1, 42.5, 41.7, 40.8 & 40.5, 39.4 & 39.2, 38.5, 34.2 & 34.1, 32.2, 24.1, 21.3; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{11}H_{19}N_2O_3$ 227.1396; Found 227.1396; LRMS *m/z* (ES) 227 (100%, MH^+).

(1RS,7RS)-9-Methyl-6-oxa-5,9-diazatricyclo[5.4.1.0^{1,5}]dodecane **22** *and (1RS,8SR)-10-Methyl-6-oxa-5,10-diazatricyclo[6.4.0.0^{1,5}]dodecane* **23**. The mixtures of cycloadducts **20** and **21** (138 mg, 0.62 mmol) in THF (2 mL) was added slowly to a solution of $LiAlH_4$ (94 mg, 2.48 mmol) in THF (6 mL). The grey suspension was then heated to 72 °C for 17 h. After the solution was cooled to room temp., the reaction was quenched with EtOAc (1 mL) and was stirred for 1 h. The light grey suspension was filtered through a sintered glass filter, and was rinsed with Et_2O (40 mL). The filtrate was concentrated to give the amines **22** and **23** (93 mg, 0.51 mmol, 80%, (3:1)) as as oil; ν_{max}/cm^{-1} 2990, 1450; R_f 0.3 [MeOH–CH_2Cl_2 (5:95)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.40 (0.75H, dd, *J* 9.0, 4.5 Hz), 3.66 (0.25H, dd, *J* 7.5, 5.0 Hz), 3.49–3.48 (1H, m), 3.43–3.41 (0.25H, m), 3.31–3.24 (1H, m), 3.02–2.95 (0.75H, m), 2.82–2.77 (0.5H, m), 2.47 (0.25H, dd, *J* 4.5, 1.5 Hz), 2.44 (0.5H, dd, *J* 4.5, 1.5 Hz), 2.41–2.30 (2.5H, m), 2.29–2.16 (1.25H, m), 2.14 (2.25H, s), 2.09 (0.75H, s), 1.80–1.73 (1.5H, m), 1.70–

1.49 (3.5H, m), 1.46–1.45 (0.75H, m), 1.44–1.42 (0.25H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 79.1, 71.6, 70.5, 70.0, 64.3, 63.3, 56.8, 56.6, 52.8, 52.6, 48.6, 47.3, 46.0, 41.3, 38.7, 37.9, 34.1, 33.9, 24.4, 21.2; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{10}H_{19}N_2O$ 183.1497; Found 183.1505; LRMS *m/z* (ES) 183 (100%, MH^+).

ASSOCIATED CONTENT

Supporting Information

Copies of NMR spectra and X-ray data (CCDC 1537946 and 1537947). This material is available free of charge via the Internet at http://pubs.acs.org.

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REFERENCES

(1) (a) Coldham, I.; Burrell, A. J. M.; White, L. E.; Adams, H.; Oram, N. *Angew. Chem. Int. Ed.* **2007**, *46*, 6159. (b) Burrell, A. J. M.; Coldham, I.; Watson, L.; Oram, N.; Pilgram, C. D.; Martin, N. G. *J. Org. Chem.* **2009**, *74*, 2290.

(2) Burrell, A. J. M.; Coldham, I.; Oram, N. *Org. Lett.* **2009**, *11*, 1515.

(3) Coldham, I.; Jana, S.; Watson, L.; Martin, N. G. *Org. Biomol. Chem.* **2009**, *7*, 1674.

(4) Furnival, R. C.; Saruengkhanphasit, R.; Holberry, H. E.; Shewring, J. R.; Guerrand, H. D. S.; Adams, H.; Coldham, I. *Org. Biomol. Chem*. **2016**, *14*, 10953.

(5) (a) Burrell, A. J. M.; Watson, L.; Martin, N. G.; Oram, N.; Coldham, I. *Org. Biomol. Chem.* **2010**, *8*, 4530; (b) Coldham, I.; Burrell, A. J. M.; Guerrand, H. D. S.; Oram, N. *Org. Lett.* **2011**, *13*, 1267. (c) Coldham, I.; Watson, L.; Adams, H.; Martin, N. G. *J. Org. Chem.* **2011**, *76*, 2360. (d) Guerrand, H. D. S.; Adams, H.; Coldham, I. *Org. Biomol. Chem.* **2011**, *9*, 7921. For similar cascade chemistry with displacement of tosylate, see (e) Siriwardena, A.; Sonawane, D. P.; Bande, O. P.; Markad, P. R.; Yonekawa, S.; Tropak, M. B.; Ghosh, S.; Chopade, B. A.; Mahuran, D. J.; Dhavale, D. D. *J. Org. Chem.* **2014**, *79*, 4398.

(6) For some reviews on spirocyclic compounds, see (a) Undheim, K. *Synthesis* **2015**, *47*, 2497. (b) Rios, R. *Chem. Soc. Rev.* **2012**, *41*, 1060. (c) Dake, G. *Tetrahedron* **2006**, *62*, 3467. (d) Pradhan, R.; Patra, M.; Behera, A. K.; Mishra, B. K.; Behera, R. K. *Tetrahedron* **2006**, *62*, 779.

(7) For some syntheses of these alkaloids, see (a) Xu, S.; Unabara, D.; Uemura, D.; Arimoto, H. *Chem. Asian J.* **2014**, *9*, 367. (b) Wu, H.; Zhang, H.; Zhao, G. *Tetrahedron* **2007**, *63*, 6454. (c) Christie, H. S.; Heathcock, C. H. *Proc. Natl. Acad. Sci.* **2004**, *101*, 12079. (d) Carson, M. W.; Kim, G.; Danishefsky. S. J. *Angew. Chem. Int. Ed. Engl.* **2001**, *40*, 4453.

(8) For some recent references, see (a) Srinivas, K.; Singh, N.; Das, D.; Koley, D. *Org. Lett.* **2017**, *19*, 274. (b) Tsukanov, S. V.; Marks, L. R.; Comins, D. L. *J. Org. Chem.* **2016**, *81*, 10433. (c) Nishikawa, N.; Kikuchi, S.; Ezaki, S.; Koyama, T.; Nokubo, H.; Kodama, T.; Tachi, Y.; Morimoto, Y. *Org. Lett.* **2015**, *17*, 5772. (d) Tabor, M. G.; Shenvi, R. A. *Org. Lett.* **2015**, *17*, 5776. (e) Pandey, G.; Janakiram, V. *Chem. Eur. J.* **2015**, *21*, 13120. (f) In, J.; Lee, S.; Kwon, Y.; Kim, S. *Chem. Eur. J.* **2014**, *20*, 17433.

(9) (a) Smith, A. C.; Cabral, S.; Kung, D. W.; Rose, C. R.; Southers, J. A.; García-Irizarry, C. N.; Damon, D. B.; Bagley, S. W.; Griffith, D. A. *J. Org. Chem.* **2016**, *81*, 3509. (b) Marson, C. M. *Chem. Soc. Rev.* **2011**, *40*, 5514. (c) Zheng, Y.; Tice, C. M.; Singh, S. B. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 3673.

(10) See, for example, (a) Snider, B. B.; Lin, H. *J. Am. Chem. Soc.* **1999**, *121*, 7778. (b) Shah, S.; Badru, R.; Singh, B. *Synth. Commun.* **2013**, *43*, 1073. (c) Das, S. N.; Chowdhury, A.; Tripathi, N.; Jana, P. K.; Mandal, S. B. *J. Org. Chem.* **2015**, *80*, 1136. (d) Rawling, M. J.;

Storr, T. E.; Bawazir, W. A.; Cully, S. J.; Lewis, W.; Makki, M. S. I. T.; Strutt, I. R.; Jones, G.; Hamza, D.; Stockman, R. A. *Chem. Commun.* **2015**, *51*, 12867. (e) Jasinski, R.; Mróz, K. Kacka, A. *J. Het. Chem.* **2016**, *53*, 1424. (f) Ma, X.-P.; Zhu, J.-F.; Wu, S.-Y.; Chen, C.-H.; Zou, N.; Liang, C.; Su, G.-F.; Mo, D.-L. *J. Org. Chem.* **2017**, *82*, 502.

(11) For a review on isoxazolidines, see Berthet, M.; Cheviet, T.; Dujardin, G.; Parrot, I.; Martinez, J. *Chem. Rev.* **2016**, *116*, 15235.

(12) (a) Robbins, D.; Newton, A. F.; Gignoux, C.; Legeay, J.-C.; Sinclair, A.; Rejzek, M.; Laxon, C. A.; Yalamanchili, S. K.; Lewis, W.; O'Connell, M. A.; Stockman, R. A. *Chem. Sci.* **2011**, *2*, 2232. (b) Arini, L. G.; Szeto, P.; Hughes, D. L.; Stockman, R. A. *Tetrahedron Lett.* **2004**, *45*, 8371. (c) Shindo M.; Fukuda, Y.; Shishido, K. *Tetrahedron Lett.* **2000**, *41*, 929. (d) Lee, S.; Zhao, Z. *Tetrahedron Lett.* **1999**, *40*, 7921. See also, (e) Wilson, M. S.; Padwa, A. *J. Org. Chem.* **2008**, *73*, 9601. (f) Flick, A. C.; Caballero, M. J. A.; Lee, H. I.; Padwa, A. *J. Org. Chem.* **2010**, *75*, 1992.

(13) (a) Grigg, R.; Markandu, J.; Surendrakumar, S.; Thornton-Pett, M.; Warnock, W. J. *Tetrahedron* **1992**, *48*, 10399. (b) Armstrong, P.; Grigg, R.; Surendrakumar, S.; Warnock, W. J. *J. Chem. Soc., Chem. Commun.* **1987**, 1327.

(14) (a) Karatholuvhu, M. S.; Sinclair, A.; Newton, A. F.; Alcaraz, M.-L.; Stockman, R. A.; Fuchs, P. L. *J. Am. Chem. Soc.* **2006**, *128*, 12656. (b) Horsley, H. T.; Holmes, A. B.; Davies, J. E.; Goodman, J. M.; Silva, M. A.; Pascu, S. I.; Collins, I. *Org. Biomol. Chem.* **2004**, *2*, 1258. (c) Williams, G. M.; Roughley, S. D.; Davies, J. E.; Holmes, A. B.; Adams, J. P. *J. Am. Chem. Soc.* **1999**, *121*, 4900.

(15) For other examples of oxime formation then cyclization and cycloaddition to give spirocyclic products, see (a) Peng, X.; Tong, B. M. K.; Hirao, H.; Chiba, S. *Angew. Chem. Int. Ed.* **2014**, *53*, 1959. (b) Frederickson, M.; Grigg, R.; Markandu, J.; Thornton-Pett, M.; Redpath, J. *Tetrahedron* **1997**, *53*, 15051. (c) Markandu, J.; Dondas, H. A.; Frederickson, M.; Grigg, R. *Tetrahedron* **1997**, *53*, 13165. (d) Dondas, H. A.; Grigg, R.; Hadjisoteriou, M.; Markandu, J.; Thomas, W. A.; Kennewell, P. *Tetrahedron* **2000**, *56*, 10087. See also (e)

Dunn, P. J.; Graham, A. B.; Grigg, R.; Saba, I. S.; Thornton-Pett, M. *Tetrahedron* **2002**, *58*, 7701. (f) Zschiesche, R.; Reissig, H.-U. *Liebigs Ann. Chem.* **1989**, 551.

(16) Eberle, M. K.; Kahle, G. G. *Tetrahedron Lett.* **1980**, *21*, 2303.

(17) Compound **2b** had the same spectroscopic data as reported in the literature: (a) Gössinger, E.; Imhof, R.; Wehrli, H. *Helv. Chim. Acta* **1975**, *58*, 96. (b) Hodges, A. J.; Adams, J. P.; Bond, A. D.; Holmes, A. B.; Press, N. J.; Roughley, S. D.; Ryan, J. H.; Saubern, S.; Smith, C. J.; Turnbull, M. D.; Newton, A. F. *Org. Biomol. Chem.* **2012**, *10*, 8963. See also (c) Yang, S.-H. Clark, G. R.; Caprio, V.; *Org. Biomol. Chem.* **2009**, *7*, 2981.

(18) Alkayar, Z. T. I.; Adams, H.; Coldham, I. *Synlett* **2016**, *27*, 447.

(19) Dumas, D. J. *J. Org. Chem.* **1988**, *53*, 4650.

(20) (a) Kulinkovich, O.; Masalov, N.; Tyvorskii, V.; De Kimpe, N.; Keppens, M. *Tetrahedron Lett.* **1996**, *37*, 1095. (b) Galeta, J.; Tenora, L.; Man, S.; Potacek, M. *Tetrahedron* **2013**, *69*, 7139.