Fsp³-Rich and Diverse Fragments Inspired by Natural Products as a Collection to Enhance Fragment-Based Drug Discovery

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SUPPORTING INFORMATION

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1. GENERAL EXPERIMENTAL PROCEDURES

Except as otherwise indicated, reactions were carried out in oven- or flame-dried glassware under nitrogen or argon with dry, freshly distilled solvents. Tetrahydrofuran was distilled from calcium hydride and LiAlH₄ in the presence of triphenyl methane. Diethyl ether was distilled from calcium hydride and LiAlH₄. CH₂Cl₂, MeOH, PhMe, MeCN and hexane were distilled from calcium hydride. All other reagents were used as supplied by commercial sources. Organic layers were dried over MgSO₄ unless otherwise stated. Yields refer to chromatographically and spectroscopically pure compounds. Thin layer chromatography was performed on glass plates coated with 60 F₂₅₄ silica. Plates were visualised using UV light (254 nm) or 1% aq KMnO₄. Retention factors (Rf) are quoted to 0.01. Flash chromatography was carried out using slurry-packed Merck 9385 Kieselgel 60 silica gel. Melting points were obtained using a Büchi Melting Point B-545 melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Spectrum One spectrometer with internal referencing as neat films. Absorption maxima (νmax) are reported in wavenumbers (cm⁻¹) and the following abbreviations are used: w, weak; m, medium; s, strong; br, broad. Proton magnetic resonance spectra were recorded at 298 K using either a 400 MHz Bruker AVANCE III HD spectrometer equipped with a Smart probe, a 500 MHz Bruker AVANCE III HD spectrometer equipped with a DCH Cryoprobe, or a 600 MHz Bruker AVANCE III spectrometer equipped with a inverse broadband probe. Whilst all compounds were formed as racemates, stereochemistry is indicated to demonstrate relative relationships between multiple stereocentres. Chemical shifts (δH) are quoted in ppm to the nearest 0.01 ppm and are referenced to the residual non-deuterated solvent peak. Coupling constants (J) are reported in Hertz to the nearest 0.5 Hz. Data are reported as follows: chemical shift, integration, multiplicity [br, broad; s, singlet; d, doublet; t, triplet; q, quartet; qui, quintet; sept, septet; m, multiplet; or as a combination of these (e.g. dd, dt, etc.)] and coupling constant(s).

Carbon magnetic resonance spectra were recorded on Bruker Avance 400 QNP (101 MHz), Bruker DRX-400 (100 MHz), Bruker Avance 500 BB ATM (125 MHz) and Bruker Avance 500 Cryo Ultrashield (125 MHz) spectrometers. Chemical shifts (δC) are quoted in ppm to the nearest 0.01 ppm, and are referenced to the deuterated solvent.

High resolution mass spectrometry (HRMS) measurements were recorded on a Micromass QTOF mass spectrometer or a Waters LCT Premier Time of Flight mass spectrometer. Mass values are quoted within the error limits of ± 5 ppm mass units. ESI refers to the electrospray ionisation technique.
2. PROCEDURES AND ANALYTICAL DATA

General Procedure A

Propargyl bromide (1.0 equiv) was added to a stirred solution of the diketone (1.0 equiv) and NaOH (1.0 equiv) in H\textsubscript{2}O (1.06 M) at rt. The resultant mixture was stirred at 60 °C for 16 h after which the aqueous layer was extracted with CH\textsubscript{2}Cl\textsubscript{2} (3 ×) and the combined organic extracts were washed with brine, then dried and concentrated \textit{in vacuo} to give a crude material.

General Procedure B

NaBH\textsubscript{4} (0.5 equiv) was added to a stirred solution of the α,α-disubstituted ketone (1.0 equiv) in DME (0.5 M) at rt. The resultant mixture was stirred at 60 °C for 24 h before 1 N HCl was added. The mixture was diluted with EtOAc, the phases were separated, and the aqueous phase was extracted with EtOAc (3 ×). The combined organic extracts were washed with brine, then dried and concentrated \textit{in vacuo} to give a crude material.

General Procedure C

Imidazole (9.5 equiv) and tert-butyldimethylsilyl chloride (5.0 equiv) were added to a stirred solution of the alcohol (1.0 equiv) in DMF (0.1 M) at rt and the resultant mixture was stirred for 24 h. H\textsubscript{2}O was added, and the aqueous phase was extracted with petroleum ether (3 ×). The combined organic extracts were dried and concentrated \textit{in vacuo} to give a crude material.

General Procedure D

TBAF (1.0 M in THF, 2 equiv) was added to a stirred solution of the silyl ether (1 equiv) in anhydrous THF (0.05 M) at rt. The reaction mixture was stirred at rt until TLC showed complete consumption of the starting material. The mixture was concentrated \textit{in vacuo} to give a crude material.

General Procedure E

10% Pd/C (20 mol%) was added to a stirred solution of the benzylamine (1.0 equiv) in EtOH (0.05 M), and the reaction mixture was stirred under an atmosphere of H\textsubscript{2} at 40 °C for 4 h. The mixture was filtered through a pad of celite and concentrated \textit{in vacuo} to give the title compound.

General Procedure F

DCC (1.35 eq.) was added to a stirred solution of \textit{syn}-1 (1.0 equiv), the carboxylic acid (1.35 equiv), and DMAP (0.1 equiv) at 0 °C in anhydrous CH\textsubscript{2}Cl\textsubscript{2} (0.1 M). The reaction mixture was stirred at rt for 16 h. Then, precipitate was filtered off and the mixture was concentrated \textit{in vacuo} to give a crude material.
2-Methyl-2-(prop-2-yn-1-yl)cyclopentane-1,3-dione (3)

According to General Procedure A, propargyl bromide (10 mL, 106 mmol), 2-methylcyclopentane-1,3-dione (10 g, 106 mmol) and NaOH (3.6 g, 106 mmol) gave a crude material. Purification via flash column chromatography (eluent hexane/EtOAc, 10:2) gave 3 as an amorphous white solid (15.9 g, 93.3 mmol, 88%). \( R_f = 0.25 \) (eluent hexane/EtOAc, 80:20); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \)H 2.90–2.75 (4H, m), 2.47 (2H, d, \( J \) 2.8), 1.98 (1H, t, \( J \) 2.5), 1.14 (3H, s); \(^13\)C NMR (101 MHz, CDCl\(_3\)): \( \delta \)C 215.0, 78.8, 70.8, 55.1, 35.6, 24.0, 19.1; IR \( \nu_{\max} \): 3280 (m, C≡C–H), 1749, 1723 (C=O). These characterisation data are in accordance with that previously reported in the literature.\(^1\)

(25\(^*\),35\(^*\))-3-Hydroxy-2-methyl-2-(prop-2-yn-1-yl)cyclopentan-1-one (syn-1) and (25\(^*\),3R\(^*\))-3-hydroxy-2-methyl-2-(prop-2-yn-1-yl)cyclopentan-1-one (anti-1)

According to General Procedure B, NaBH\(_4\) (630 mg, 16.5 mmol) and 3 (5.0 g, 33.3 mmol) gave a crude material. Purification via flash column chromatography (eluent hexane/EtOAc, 80:20) gave syn-1 (1.78 g, 11.7 mmol, 35%) and anti-1 (1.16 g, 7.66 mmol, 23%) both as colourless oils.

Data of syn-1:
\( R_f = 0.19 \) (eluent hexane/EtOAc, 80:20); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \)H 4.27 (1H, dd, \( J \) 4.6, 1.9), 2.56–2.32 (4H, m), 2.23 (1H, ddd, \( J \) 13.9, 10.3, 9.2, 4.5), 2.09–1.99 (2H, m), 1.96 (1H, br s), 1.12 (3H, s); \(^13\)C NMR (101 MHz, CDCl\(_3\)): \( \delta \)C 219.7, 81.2, 77.0, 70.8, 53.3, 34.3, 27.6, 21.1, 20.1; IR \( \nu_{\max} \): 3435 (br, O–H), 3289 (m, C≡C–H), 3280 (m, C≡C–H), 1729 (s, C=O).

Data of anti-1:
\( R_f = 0.17 \) (eluent hexane/EtOAc, 80:20); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \)H 4.41 (1H, ddd, \( J \) 9.5, 6.4, 3.5), 2.59–2.24 (4H, m), 2.22–2.09 (2H, m), 2.05 (1H, t, \( J \) 2.7), 1.93–1.79 (1H, m), 1.06 (3H, s); \(^13\)C NMR (101 MHz, CDCl\(_3\)): \( \delta \)C 218.4, 80.8, 75.7, 71.3, 51.8, 35.0, 27.3, 25.1, 15.2; IR \( \nu_{\max} \): 3439 (br, O–H), 3287 (m, C≡C–H), 1731 (s, C=O).

These characterisation data are in accordance with that previously reported in the literature.\(^1\)
2-Methyl-2-(prop-2-yn-1-yl)cyclohexane-1,3-dione (6)

According to General Procedure A, propargyl bromide (6 mL, 53.5 mmol), 2-methylcyclohexane-1,3-dione (6.75 g, 53.5 mmol) and NaOH (2.14 g, 53.5 mmol) gave a crude material. Purification via flash column chromatography (elucent hexane/EtOAc, 10:2) gave 6 as a yellow oil (6.14 g, 37.5 mmol, 70%). \( R_f = 0.27 \) (elucent hexane/EtOAc, 80:20); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 2.73–2.52 (6H, m), 2.02–1.80 (3H, m), 1.24 (3H, s); \(^13\)C NMR (101 MHz, CDCl\(_3\)): \( \delta \) C 208.8, 80.4, 70.5, 64.0, 38.1, 24.3, 22.3, 17.2; IR \( \nu_{\text{max}} \): 3276 (m, C≡C–H), 1728, 1694 (C=O). These characterisation data are in accordance with that previously reported in the literature.

(2S*,3S*)-3-Hydroxy-2-methyl-2-(prop-2-yn-1-yl)cyclohexan-1-one (syn-8) and (2S*,3R*)-3-hydroxy-2-methyl-2-(prop-2-yn-1-yl)cyclohexan-1-one (anti-8)

According to General Procedure B, NaBH\(_4\) (680 mg, 18.0 mmol) and 6 (5.88 g, 35.8 mmol) gave a crude material. Purification via flash column chromatography (elucent hexane/EtOAc, 80:20) gave syn-8 (2.26 g, 13.6 mmol, 38%) and anti-8 (1.84 g, 11.1 mmol, 31%) both as colourless oils.

Data of syn-8:
\( R_f = 0.19 \) (elucent hexane/EtOAc, 80:20); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) H 4.19 (1H, m), 2.69 (1H, dd, \( J = 17.3, 2.7 \)), 2.59–2.41 (2H, m), 2.37–2.29 (1H, m), 2.15–2.02 (2H, m), 2.01 (1H, t, \( J = 2.7 \)), 1.94 (1H, d, \( J = 4.0 \)), 1.92–1.76 (2H, m), 1.27 (3H, s); \(^13\)C NMR (101 MHz, CDCl\(_3\)): \( \delta \) C 213.1, 81.2, 75.1, 71.3, 52.5, 37.8, 28.2, 23.0, 21.3, 20.7; IR \( \nu_{\text{max}} \): 3505 (br, O–H), 3393 (s, C≡C–H), 1702 (s, C=O).

Data of anti-8:
\( R_f = 0.16 \) (elucent hexane/EtOAc, 80:20); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) H 4.07 (1H, dd, \( J = 10.3, 3.8 \)), 2.60 (1H, d, \( J = 16.8 \)), 2.52–2.41 (2H, m), 2.33–2.26 (2H, m), 2.07–1.91 (3H, m), 1.91–1.79 (1H, m), 1.63–1.50 (1H, m), 1.24 (3H, s); \(^13\)C NMR (101 MHz, CDCl\(_3\)): \( \delta \) C 211.9, 81.7, 74.7, 71.5, 54.4, 37.3, 29.2, 24.9, 20.16, 17.3; IR \( \nu_{\text{max}} \): 3448 (br, O–H), 3289 (s, C≡C–H), 1702 (s, C=O).

These characterisation data are in accordance with that previously reported in the literature.\(^1\)
2-(Cyclopropylmethyl)cyclopentane-1,3-dione (5)

[Image of the structure of 5]

L-Proline (37.4 mg, 0.325 mmol) was added to a stirred suspension of cyclopentane-1,3-dione (638 mg, 6.50 mmol), cyclopropanecarboxaldehyde (1.46 mL, 19.5 mmol) and hantzsch ester (1.66 g, 6.57 mmol) in anhydrous CH₂Cl₂ (25 mL) at rt. The resultant mixture was stirred at rt for 24 h, the concentrated in vacuo. Purification via flash column chromatography (EtOAc/petroleum ether/AcOH, 90:10:2) gave 5 as a light orange solid (899 mg, 5.92 mmol, 91%). \( R_f = 0.38 \) (EtOAc/AcOH, 98:2); \(^1\)H NMR (400 MHz, DMSO-\(d_6\)): δ\(_H\) 11.45 (1H, s), 2.35 (4H, s), 1.93 (2H, d, \( J = 6.6 \)), 0.88–0.71 (1H, m), 0.35–0.19 (2H, m), 0.06–0.02 (2H, m); \(^13\)C NMR (101 MHz, DMSO-\(d_6\)): δ\(_C\) 115.9, 25.0, 9.9, 4.2, 4 x C (cyclopentadione) not seen; IR \( \nu_{max} \): 2500 (br, O–H), 1673 (s, C=O); HRMS (ESI): [M+H]+ calcd. for C\(_9\)H\(_{13}\)O\(_2\): 153.0916, found: 153.0918.

2-(Cyclopropylmethyl)-2-(prop-2-yn-1-yl)cyclopentane-1,3-dione (7)

[Image of the structure of 7]

According to General Procedure A, propargyl bromide (0.295 mL, 2.73 mmol), 3 (416 mg, 2.73 mmol) and NaOH (147 mg, 2.73 mmol) gave a crude material. Purification via flash column chromatography (elucent Petroleum ether/EtOAc, 86:14) gave 7 as a colourless oil (336 mg, 1.77 mmol, 65%). \( R_f = 0.32 \) (petroleum ether/EtOAc, 86:14); \(^1\)H NMR (400 MHz, CDCl₃): δ\(_H\) 2.92–2.67 (4H, m), 2.41 (2H, d, \( J = 2.6 \)), 1.91 (1H, t, \( J = 2.6 \)), 1.55 (2H, d, \( J = 7.1 \)), 0.59–0.41 (1H, m), 0.42–0.32 (2H, m), 0.06–0.05 (2H, m); \(^13\)C NMR (101 MHz, CDCl₃): δ\(_C\) 216.5, 78.9, 70.7, 60.1, 40.5, 37.1, 23.9, 6.9, 4.9; IR \( \nu_{max} \): 3278 (s, C≡C–H), 1719 (s, C=O); HRMS (ESI): calcd. for C\(_{12}\)H\(_{15}\)O\(_2\) [M+H]+: 191.1072, found: 191.1071.
(2S*,3R*)-2-(Cyclopropylmethyl)-3-hydroxy-2-(prop-2-yn-1-yl)cyclopentan-1-one (anti-9) and (2S*,3S*)-2-(cyclopropylmethyl)-3-hydroxy-2-(prop-2-yn-1-yl)cyclopentan-1-one (syn-9)

According to General Procedure B, NaBH₄ (35.0 mg, 0.925 mmol) and 7 (320 mg, 1.68 mmol) gave a crude material. Purification via flash column chromatography (CH₂Cl₂/EtOAc, 99:1 to 95:5) gave anti-9 (174.2 mg, 0.91 mmol, 54%) and syn-9 (62.6 mg, 0.32 mmol, 19%) both as colourless oils.

Data for anti-9
Rᶠ = 0.41 (CH₂Cl₂/EtOAc, 9:1); ¹H NMR (400 MHz, CDCl₃): δₕ 4.42 (1H, ddd, J 9.8, 7.0, 3.0), 2.67 (1H, dd, J 17.0, 2.6), 2.51 (1H, ddd, J 19.3, 10.0, 2.6), 2.38–2.23 (3H, m), 2.23–2.08 (1H, m), 2.06 (1H, t, J 2.7), 1.97 (1H, dq, J 12.5, 9.8), 1.74 (1H, dd, J 14.7, 5.4), 1.40 (1H, dd, J 14.7, 8.3 Hz), 1.31 (2H, m), 1.16–0.96 (4H, m), 0.90 (3H, dtt, J 13.3, 8.3, 5.1), 0.56–0.36 (2H, m), 0.28 (1H, dq, J 12.5, 4.8), 0.14 (1H, dd, J 14.7, 8.3); ¹³C NMR (101 MHz, CDCl₃): δC 218.0, 81.3, 76.5, 71.5, 55.2, 35.1, 33.4, 27.1, 23.3, 5.9, 5.4, 4.8; IR νmax: 3452 (br, O–H), 3287 (s, C≡C–H), 1729 (s, C=O); HRMS (ESI): [M+H]+ calcd. for C₁₂H₁₇O₂+: 193.1229, found: 193.1225.

Data for syn-9
Rᶠ = 0.37 (CH₂Cl₂/EtOAc, 9:1); ¹H NMR (400 MHz, CDCl₃): δₕ 4.34 (1H, dq, J 5.0, 3.0), 2.70 (1H, dd, J 17.0, 2.7), 2.56–2.24 (4H, m), 2.12 (1H, d, J 3.6), 2.09–1.99 (2H, m), 1.58 (1H, dd, J 14.5, 5.9), 1.43 (1H, dd, J 14.5, 7.8), 0.65 (1H, dq, J 7.9, 5.1), 0.55–0.39 (2H, m), 0.28 (1H, ddd, J 7.3, 4.3, 3.5), –0.01 (1H, dtt, J 9.5, 4.8, 3.5); ¹³C NMR (151 MHz, CDCl₃): δC 219.0, 81.6, 75.5, 71.0, 57.4, 37.9, 35.0, 27.7, 19.0, 6.2, 5.0, 4.6; IR νmax: 3453 (br, O–H), 3303 (s, C≡C–H), 1732 (s, C=C–H), 1729 (s, C=O); HRMS (ESI): [M+H]+ calcd. for C₁₅H₂₇O₂Si+: 267.1775, found: 267.1775.

(2S*,3S*)-3-((tert-Butyldimethylsilyl)oxy)-2-methyl-2-(prop-2-yn-1-yl)cyclopentan-1-one (syn-S1)

According to General Procedure C, imidazole (811 mg, 11.9 mmol), tert-butyldimethylsilyl chloride (939 mg, 6.23 mmol) and syn-1 (190 mg, 1.25 mmol) gave a crude material. Purification via flash column chromatography (elucent hexane/EtOAc, 90:10) gave syn-S1 as a colourless oil (327 mg, 1.23 mmol, 98%). Rᶠ = 0.42 (elucent hexane/EtOAc, 90:10); ¹H NMR (400 MHz, CDCl₃): δₕ 4.15 (1H, m), 2.49–2.30 (4H, m), 2.17 (1H, m), 1.95 (2H, m), 1.09 (3H, s), 0.87 (9H, s), 0.12 (3H, s), 0.11 (3H, s); ¹³C NMR (101 MHz, CDCl₃): δC 219.5, 81.6, 76.8, 70.1, 53.7, 33.6, 28.1, 25.7, 20.6, 19.2, 18.0, –4.5, –5.0; IR νmax: 3307 (s, C=C–H), 2930 (m, C–H), 1744 (s, C=O); HRMS (ESI): [M+H]+ calcd. for C₁₅H₂₇O₂Si+: 267.1775, found: 267.1775.
According to General Procedure C, imidazole (427 mg, 6.23 mmol), tert-butyldimethylsilyl chloride (494 mg, 3.28 mmol) and anti-1 (100 mg, 0.66 mmol) gave a crude material. Purification via flash column chromatography (eluent hexane/EtOAc, 90:10) gave anti-S1 as a colourless oil (167 mg, 0.63 mmol, 95%). 

\[
\text{R}_f = 0.42 \text{ (eluent hexane/EtOAc, 90:10)}; \quad \text{\textsuperscript{1}H NMR (400 MHz, CDCl}_3) : \delta_H 4.50–4.42 (1H, m), 2.53–2.35 (2H, m), 2.18–2.06 (3H, m), 1.95 (1H, t, J 2.6), 1.88–1.73 (1H, m), 0.96 (3H, s), 0.89 (9H, s), 0.10 (6H, 2 × s); \quad \text{\textsuperscript{13}C NMR (101 MHz, CDCl}_3) : \delta_C 218.6, 80.7, 74.4, 70.7, 53.0, 35.6, 28.5, 25.9, 24.5, 18.1, 16.2, –4.3, –4.8; \quad \text{IR } \nu_{\text{max}}: 3309 \text{ (s, } \text{C≡C–H}), 2930 \text{ (s, } \text{C–H}), 1747 \text{ (s, } \text{C=O}); \quad \text{HRMS (ESI): } [\text{M+H}]^+ \text{ calcd. for C}_{15}H_{27}O_2Si^+: 267.1775, \text{ found: 267.1775.}
\]

(25\textsuperscript{°},3R\textsuperscript{°},5R\textsuperscript{°})-3-((tert-Butyldimethylsilyl)oxy)-2-methyl-2-(prop-2-yn-1-yl)cyclopentan-1-one (10)

To a solution of anti-S1 (86 mg, 0.322 mmol) in anhydrous THF (6.6 mL) was added LiHMDS (1.0 M in PhMe, 0.39 mL, 0.39 mmol) at –78 °C and the mixture was stirred for 30 min. Then, cooling was removed and the mixture was allowed to warm to rt. After stirring 30 min at rt, the mixture was cooled to 0 °C and allyl bromide (33.6 µL, 0.39 mmol) was added. The reaction mixture was stirred at 0 °C for 1 h, then concentrated in vacuo and filtered through a short silica plug (eluent EtOAc/petroleum ether 2:98) to give a crude material as a mixture of diastereomers (76:24 dr).

Hoveyda-Grubbs 2\textsuperscript{nd} generation catalyst (12.5 mg, 20.0 µmol) was added to a stirred solution of the crude product in anhydrous PhMe (40 mL) at rt. The reaction mixture was stirred under an ethylene atmosphere at reflux for 3 h. The mixture was concentrated in vacuo and filtered through a short plug of silica. TBAF (1.0 M in THF, 0.103 mL, 0.103 mmol) was added to a solution of the crude product in anhydrous THF (3 mL). The solution was stirred at rt for 2 h, then concentrated in vacuo. Purification via flash column chromatography (petroleum ether/EtOAc, 66:33) gave 10 as a colourless oil (8.0 mg, 41.7 µmol, 13% over three steps). 

\[
\text{R}_f = 0.45 \text{ (petroleum ether/EtOAc, 50:50)}; \quad \text{\textsuperscript{1}H NMR (600 MHz, CDCl}_3) : \delta_H 6.30 (1H, dd, J 17.5, 11.0), 5.69 (1H, dd, J 6.6, 3.2), 5.06 (1H, d, J 17.5), 4.93 (1H, d, J 11.0), 4.06 (1H, dd, J 6.9, 2.4), 2.77 (1H, dt, J 9.0, 4.0), 2.47 (1H, d, J 18.4), 2.43–2.32 (2H, m), 2.15 (ddd, J 14.5, 6.9, 4.0 Hz, 1H), 2.03–1.98 (1H, m), 1.96 (1H, ddd, J 14.5, 9.0, 2.5), 1.61 (1H, br s), 1.22 (3H, s); \quad \text{\textsuperscript{13}C NMR (151 MHz, CDCl}_3) : \delta_C 206.3, 142.8, 135.7, 129.4, 110.9, 76.3, 53.3, 44.6, 37.3, 35.5, 33.5, 17.1; \quad \text{IR } \nu_{\text{max}}: 3397 \text{ (br., } \text{O–H}), 1733 \text{ (s, } \text{C=O}); \quad \text{HRMS (ESI): } [\text{M+H}]^+ \text{ calcd. for C}_{12}H_{17}O_2Si^+: 193.1223, \text{ found: 193.1232.}
\]
(25R,3R)-3-[(tert-Butyldimethylsilyl)oxy]-2-methyl-5-methylene-2-(prop-2-yn-1-yl)cyclopentan-1-one (11)

\[
\begin{align*}
\text{TBSO} & \quad \text{O} \\
\text{CH}_2\text{Br}_2 & (0.868 \text{ mL}, 12.4 \text{ mmol}) \text{ and } \text{Et}_3\text{NH} & (2.56 \text{ mL}, 24.8 \text{ mmol}) \text{ were added to a stirred solution of } \text{anti-\text{S}1} & (550 \text{ mg}, 2.06 \text{ mmol}) \text{ in } \text{CH}_2\text{Cl}_2 & (10 \text{ mL}). \text{ The mixture was heated under microwave irradiation at } 125 \degree \text{C for 20 min.} \text{ The mixture was diluted with } \text{Et}_2\text{O} & (150 \text{ mL}) \text{ and precipitate was removed by filtration, the filtrate was then concentrated } \text{in vacuo}. \text{ Purification via flash column chromatography (petroleum ether/EtOAc, 97:3) gave } 11 \text{ as a colourless oil (389 mg, 1.40 mmol, 68%). } R_f = 0.20 \text{ (petroleum ether/EtOAc, 97:3); } ^1\text{H NMR (400 MHz, CDCl}_3) : \delta_H \text{ 6.11 (1H, ddd, J = 3.1, 2.0, 1.1), 5.37 (1H, ddd, J = 3.1, 2.0, 1.1), 4.46 (1H, dd, J = 8.0, 6.9), 2.89 (1H, ddt, J = 16.5, 6.9, 2.0), 2.60–2.49 (1H, m), 2.48 (1H, dd, J = 16.9, 2.7), 2.23 (1H, dd, J = 16.9, 2.7), 1.95 (1H, t, J = 2.7), 1.02 (3H, s), 0.90 (9H, s), 0.11 (6H, app s); } ^13\text{C NMR (101 MHz, CDCl}_3) : \delta_C \text{ 206.2, 142.2, 119.6, 80.7, 72.0, 70.8, 53.4, 36.4, 25.9, 24.3, 18.1, 16.4. } \text{IR } \nu_{\max} : 3313, (\text{m, C≡C–H}), 1730 (\text{s, C=O}), 1641 (\text{s, C=C}), \text{ HRMS (ESI): [M + H]^+ calcd. for C}_{16}\text{H}_{27}\text{O}_2\text{Si}^+: 279.1775, \text{ found 279.1767.}
\end{align*}
\]

Ethyl (5S*,7S*,8R*)-8-[(tert-Butyldimethylsilyl)oxy]-7-methyl-6-oxo-7-(prop-2-yn-1-yl)-2-oxa-3-azaspiro[4.4]non-3-ene-4-carboxylate (S2)

\[
\begin{align*}
\text{TBSO} & \quad \text{EtO}_2\text{N} \\
\text{1-Ethyl oxalyl chloride 2-oxime (56.2 mg, 0.371 mmol) in anhydrous CH}_2\text{Cl}_2 & (5 \text{ mL}) \text{ was added dropwise over 1 h to a stirred solution of } 11 & (86.0 \text{ mg, 0.309 mmol}) \text{ and Et}_3\text{N} & (52.0 \mu\text{L}, 0.371 mmol) \text{ in anhydrous CH}_2\text{Cl}_2 & (5 \text{ mL}). \text{ The mixture was then concentrated } \text{in vacuo}. \text{ Purification via flash column chromatography (petroleum ether/EtOAc, 90:10) gave } S2 \text{ as a colourless oil (85.0 mg, 0.216 mmol, 70%). } R_f = 0.33 \text{ (petroleum ether/EtOAc, 90:10); } ^1\text{H NMR (400 MHz, CDCl}_3) : \delta_H \text{ 4.55 (1H, t, J = 5.5), 4.34 (2H, q, J = 7.1), 3.49 (1H, d, J = 18.0), 3.14 (1H, d, J = 18.0), 2.61 (1H, dd, J = 14.4, 5.5), 2.45 (1H, dd, J = 17.1, 2.6), 2.28 (1H, dd, J = 17.1, 2.6), 2.14–2.04 (2H, m), 1.36 (3H, t, J = 7.1), 1.11 (3H, s), 0.89 (9H, s), 0.11 (6H, app s); } ^13\text{C NMR (101 MHz, CDCl}_3) : \delta_C \text{ 213.3, 160.1, 150.7, 90.1, 79.1, 72.0, 71.8, 62.4, 52.7, 42.8, 42.6, 25.9, 25.1, 18.1, 16.7, 14.2, –4.4, –4.8; } \text{IR } \nu_{\max} : 3297, (\text{m, C≡C–H}), 1730, (\text{s, C=O}), 1721, (\text{s, C=C}), 1642, (\text{m, C=CH}_2); \text{ HRMS (ESI): [M + H]^+ calcd. for C}_{20}\text{H}_{32}\text{NO}_5\text{Si}^+: 394.2044, \text{ found 394.2044.}
\end{align*}
\]
Ethyl \((SS^*,7S^*,8R^*)\)-8-hydroxy-7-methyl-6-oxo-7-\{(prop-2-yn-1-yl)\}-2-oxa-3-azaspiro[4.4]nonan-3-ene-4-carboxylate (12)

According to General Procedure D, S2 (29.0 mg, 73.7 µmol) and TBAF (1.0 M in THF, 0.111 mL, 0.111 mmol) gave a crude material. Purification via flash column chromatography (EtOAc/petroleum ether 2:3) gave 12 as a colourless oil (9.0 mg, 32.4 µmol, 44%). \( R_f = 0.42 \) (EtOAc/petroleum ether 1:1); \(^1\)H NMR (600 MHz, CDCl\(_3\)): \( \delta \) 4.60 (1H, ddd, \( J \) 8.1, 6.1, 3.3), 4.35 (2H, qd, \( J \) 7.2, 0.7), 3.53 (1H, d, \( J \) 18.0), 3.17 (1H, d, \( J \) 18.0), 2.70 (1H, dd, \( J \) 14.4, 6.1), 2.49–2.40 (2H, m), 2.12 (1H, t, \( J \) 2.7), 2.10 (1H, d, \( J \) 3.3), 2.08–2.03 (1H, m), 1.36 (3H, t, \( J \) 7.2), 1.18 (3H, s); \(^{13}\)C NMR (151 MHz, CDCl\(_3\)): \( \delta \) 212.5, 160.0, 150.9, 90.1, 79.8, 73.0, 71.9, 62.5, 51.0, 41.1, 40.8, 25.9, 15.9, 14.3; IR \( \nu_{\text{max}} \): 3506 (br. O–H), 3281 (m, C≡C–H), 1752 (s, C=O), 1721 (s, C=O), 1598 (m, C=N); HRMS (ESI): [M + Na]\(^+\) calcd. for C\(_{14}\)H\(_{17}\)NO\(_5\)Na\(^+\): 302.0999, found 302.1002.

\((SS^*,7S^*,8R^*)\)-2-Benzyl-8-\{(tert-butyldimethylsilyl)oxy\}-7-methyl-7-\{(prop-2-yn-1-yl)\}-2-azaspiro[4.4]nonan-6-one (S3a) and \((5R^*,7S^*,8R^*)\)-2-benzyl-8-\{(tert-butyldimethylsilyl)oxy\}-7-methyl-7-\{(prop-2-yn-1-yl)\}-2-azaspiro[4.4]nonan-6-one (S3b)

\( N\)-(methoxymethyl)-\( N\)-(trimethylsilylmethyl)benzylamine (90%, 0.122 mL, 0.427 mmol) and TFA (0.1 M in CH\(_2\)Cl\(_2\), 0.355 mL, 35.6 µmol) were added to a stirred solution of 11 (99.0 mg, 0.356 mmol) in CH\(_2\)Cl\(_2\) (7 mL). The reaction mixture was stirred at 0°C for 1 h, then concentrated \( \text{in vacuo} \) to give a mixture of diastereomers (66:43 \text{dr}). Purification via flash column chromatography (petroleum ether/EtOAc, 80:20) gave S3a (89.9 mg, 0.219 mmol, 61%) and S3b (47.5 mg, 0.116 mmol, 32%) both as yellow oils.

Data of S3a:
\( R_f = 0.54 \) (petroleum ether/EtOAc, 80:20); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 7.37–7.19 (5H, m), 4.37 (1H, dd, \( J \) 8.4, 6.1), 3.72–3.56 (2H, m), 2.85 (1H, td, \( J \) 8.4, 7.5, 4.2), 2.64–2.50 (3H, m), 2.39 (1H, dd, \( J \) 16.9, 2.7), 2.31 (1H, dd, \( J \) 13.0, 6.1), 2.22 (1H, dd, \( J \) 12.5, 8.0, 4.2), 2.13 (1H, dd, \( J \) 16.9, 2.7), 1.90 (1H, dd, \( J \) 13.0, 8.4), 1.84–1.73 (2H, m), 0.98 (3H, s), 0.90 (9H, s), 0.10 (3H, s), 0.08 (3H, s); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)): \( \delta \) 221.9, 139.1, 128.8, 128.4, 127.1, 80.9, 72.4, 70.8, 64.0, 59.8, 54.5, 54.4, 53.5, 44.5, 37.2, 25.9, 25.0, 18.2, 17.1, –4.3, –4.8; IR \( \nu_{\text{max}} \): 3311 (m, C=C–H), 1737 (s, C=O); HRMS (ESI): [M + H]\(^+\) calcd. for C\(_{25}\)H\(_{38}\)NO\(_2\)Si\(^+\): 412.2667, found 412.2667.
Data of S3b:
Rf = 0.36 (petroleum ether/EtOAc, 80:20); $^1$H NMR (400 MHz, CDCl$_3$): δ$_H$ 7.37–7.16 (5H, m), 4.44 (1H, dd, J 7.8, 5.9), 3.70 (1H, d, J 12.8), 3.58 (1H, d, J 12.8), 2.86 (1H, ddd, J 9.0, 7.3, 4.2), 2.68 (2H, d, J 2.4), 2.55 (1H, dt, J 9.0, 7.8), 2.42 (1H, dd, J 16.9, 2.7), 2.25–2.08 (3H, m), 1.64 (1H, dt, J 12.6, 7.5), 0.94 (3H, s), 0.86 (9H, s), 0.08 (3H, s), 0.07 (3H, s); $^{13}$C NMR (101 MHz, CDCl$_3$): δ$_C$ 221.7, 139.1, 128.9, 128.4, 127.1, 81.0, 128.4, 127.1, 81.0, 72.2, 70.9, 64.2, 60.2, 54.4, 54.1, 53.6, 44.6, 37.5, 25.9, 25.1, 18.1, 16.9, −4.3, −4.8; IR $v_{\max}$: 3311 (m, C≡C–H), 1737 (s, C=O);
HRMS (ESI): [M + H]$^+$ calcd. for C$_{25}$H$_{38}$NO$_2$Si$: 412.2667, found 412.2666.

(5S*,7S*,8R*)-2-Benzyl-8-hydroxy-7-methyl-7-(prop-2-yn-1-yl)-2-azaspiro[4.4]nonan-6-one (S4a)

According to General Procedure D, S3a (67.0 mg, 0.163 mmol) and TBAF (1.0 M in THF, 0.326 mL, 0.326 mmol) gave a crude material. Purification via flash column chromatography (EtOAc) gave S4a as a yellow oil (46.0 mg, 0.155 mmol, 95%). Rf = 0.28 (EtOAc); $^1$H NMR (600 MHz, CDCl$_3$): δ$_H$ 7.35–7.19 (5H, m), 4.32 (1H, dd, J 9.9, 6.5), 3.65 (1H, d, J 13.0), 3.61 (1H, d, J 13.0), 2.93–2.85 (1H, m), 2.60–2.53 (2H, m), 2.46 (1H, dd, J 12.9, 6.5), 2.41 (1H, d, J 9.3), 2.38–2.27 (3H, m), 2.24 (1H, dt, J 8.2, 4.4), 1.93 (1H, t, J 2.6), 1.87 (1H, dd, J 12.9, 9.9), 1.79 (1H, dt, J 12.9, 7.7), 1.05 (3H, s); $^{13}$C NMR (101 MHz, CDCl$_3$): δ$_C$ 221.8, 154.6, 128.8, 128.4, 127.2, 81.0, 73.4, 71.2, 64.3, 59.8, 54.4, 54.1, 53.6, 43.4, 36.7, 25.6, 16.0; IR $v_{\max}$: 3370 (br s, O–H), 3291 (m, C≡C–H), 1735 (s, C=O); HRMS (ESI): [M + H]$^+$ calcd. for C$_{19}$H$_{24}$NO$_2$: 298.1802, found 298.1805.

(5S*,7S*,8R*)-8-Hydroxy-7-methyl-7-propyl-2-azaspiro[4.4]nonan-6-one (13a)

According to General Procedure E, S4a (30.0 mg, 0.101 mmol) and 10% Pd/C (21.5 mg, 20.2 µmol) gave 13a as an off-white amorphous solid (20.8 mg, 99.0 µmol, 98%). $^1$H NMR (400 MHz, CD$_3$OD): δ$_H$ 4.15 (1H, dd, J 7.2, 5.9), 3.09 (1H, ddd, J 11.4, 8.3, 5.6), 3.00 (1H, dt, J 11.4, 7.4), 2.88 (1H, d, J 11.5), 2.76 (1H, d, J 11.5), 2.29 (1H, dd, J 13.2, 5.9), 2.12 (1H, ddd, J 13.0, 8.3, 6.9), 1.95 (1H, dd, J 13.2, 7.2), 1.83 (1H, ddd, J 13.0, 7.7, 5.6), 1.45–1.30 (4H, m), 1.24–1.14 (1H, m), 0.99 (3H, s), 0.91 (3H, t, J 7.0); $^{13}$C NMR (101 MHz, CD$_3$OD): δ$_C$ 226.0, 73.8, 58.3, 56.4, 55.1, 47.7, 42.1, 39.9, 39.0, 18.5, 16.7, 15.0; IR $v_{\max}$: 3299 (br s, O–H), 1727 (s, C=O); HRMS (ESI): [M + H]$^+$ calcd. for C$_{12}$H$_{22}$NO$_2$: 212.1651, found 212.1648.
(5R*,7S*,8R*)-2-Benzyl-8-hydroxy-7-methyl-7-(prop-2-yn-1-yl)-2-azaspiro[4.4]nonan-6-one (S4b)

According to General Procedure D, S3b (43.0 mg, 0.104 mmol) and TBAF (1.0 M in THF, 0.209 mL, 0.209 mmol) gave a crude material. Purification via flash column chromatography (EtOAc) S4b as a yellow oil (24.5 mg, 82.5 µmol, 79%). Rf = 0.22 (EtOAc); 1H NMR (400 MHz, CDCl3) δ H 7.36–7.28 (4H, m), 7.27–7.21 (1H, m), 4.43 (1H, dd, J 9.6, 6.4), 3.72–3.58 (2H, m), 2.83 (1H, ddd, J 9.2, 7.1, 4.5), 2.76 (1H, d, J 9.6), 2.66 (1H, d, J 9.6), 2.57 (1H, dt, J 9.2, 7.4), 2.39–2.31 (3H, m), 2.10 (1H, br s), 2.06–1.89 (3H, m), 1.68 (1H, dt, J 12.5, 7.4), 1.01 (3H, s); 13C NMR (100 MHz, CDCl3) δ C 221.3, 139.1, 128.8, 128.4, 127.1, 81.1, 72.9, 71.3, 60.1, 54.2, 54.0, 52.1, 43.5, 38.0, 25.7, 15.8; IR νmax: 3331 (br s, O–H), 3285 (m, C≡C–H), 1735 (s, C=O); HRMS (ESI): [M + H]+ calcd. for C19H25NO2+: 298.1802, found 298.1799.

(5R*,7S*,8R*)-8-Hydroxy-7-methyl-7-propyl-2-azaspiro[4.4]nonan-6-one (13b)

According to General Procedure E, S4b (20.0 mg, 67.3 µmol) and 10% Pd/C (14.3 mg, 13.5 µmol) gave 13b as an off-white amorphous solid (14.0 mg, 66.4 µmol, 99%). 1H NMR (400 MHz, CD3OD) δ H 4.19 (1H, t, J 5.4), 3.49–3.35 (3H, m), 3.26 (1H, d, J 12.1), 2.41 (1H, dd, J 13.6, 5.4), 2.19–1.97 (3H, m), 1.48–1.40 (2H, m), 1.02 (3H, s), 0.92 (3H, t, J 7.2); 13C NMR (101 MHz, CD3OD) δ C 223.0, 73.9, 55.6, 55.0, 54.0, 46.3, 40.4, 39.0, 36.5, 18.5, 16.2, 14.9; IR νmax: 3364 (br, s, O–H), 1733 (s, C=O); HRMS (ESI): [M + H]+ calcd. for C12H22NO2+: 212.1651, found 212.1645.

(4R*,5S*)-4-((tert-Butyldimethylsilyl)oxy)-5-methyl-5-(prop-2-yn-1-yl)cyclopent-2-en-1-one (14)

IBX (45% wt., 460 mg, 0.74 mmol) was added to a stirred solution of S1 (100 mg, 0.37 mmol) in a mixture of fluorobenzene (1.70 mL) and DMSO (0.85 mL), and the resultant solution was stirred at 65 °C for 24 h. The reaction mixture was cooled to room temperature and diluted with ether (100 mL) and then washed successively with satd. NaHCO3, H2O and brine. The organic layer was then dried and concentrated in vacuo. Purification via flash column chromatography (hexane/EtOAc, 99:1) gave 14 as a colourless oil (45 mg, 0.17 mmol, 45%). Rf = 0.15 (eluent hexane/EtOAc, 99:1); 1H NMR (400 MHz, CD2Cl2): δ H 7.37 (1H, dd, J 5.9, 2.1), 6.17 (1H dd, J 5.9, 1.7), 4.94 (1H, app t, J 1.7), 2.48 (1H, dd, J 16.9, 2.7), 2.30 (dd, J 16.9, 2.7), 1.92 (t, J 2.7), 1.04 (3H, s), 0.93 (9H, s), 0.17
(3aS*,5S*,6R*,6aR*)-2-Benzyl-6-(((tert-butyldimethylsilyl)oxy)-5-methyl-5-(prop-2-yn-1-yl)hexahydrocyclopenta[c]pyrrol-4(1H)-one (S5a) and (3aR*,5S*,6R*,6aS*)-2-benzyl-6-((tert-butyldimethylsilyl)oxy)-5-methyl-5-(prop-2-yn-1-yl)hexahydrocyclopenta[c]pyrrol-4(1H)-one (S5b)

N-(methoxymethyl)-N-(trimethylsilylmethyl)benzylamine (90%, 51.6 µL, 0.181 mmol) and TFA (0.1 M in CH₂Cl₂, 0.151 mL, 15.1 µmol) were added to a stirred solution of 14 (40 mg, 0.151 mmol) in CH₂Cl₂ (3 mL). The reaction mixture was stirred at rt for 1 h, then concentrated in vacuo to give a mixture of diastereomers (55:54 dr). Purification via flash column chromatography (petroleum ether/EtOAc, 95:5) gave S5a (18.0 mg, 45.3 µmol, 30%) and S5b (15.0 mg, 37.7 µmol, 25%) both as yellow oils.

Data of S5a:

\[ R_f = 0.46 \] (petroleum ether/EtOAc, 90:10); \[ ^1H \text{ NMR} (400 MHz, CDCl₃) \]: δH 7.33–7.15 (5H, m), 4.37 (1H, d, \( J = 6.3 \)), 3.69 (1H, d, \( J = 13.4 \)), 3.46 (1H, d, \( J = 13.4 \)), 3.19 (1H, d, \( J = 9.2 \)), 3.00 (2H, t, \( J = 9.2 \)), 2.90 (1H, d, \( J = 9.2 \)), 2.64–2.54 (2H, m), 2.31–2.23 (2H, m), 2.16 (1H, dd, \( J = 16.9, 2.7 \)), 2.01 (1H, t, \( J = 2.7 \)), 1.02 (3H, s), 0.88 (3H, s), 0.07 (3H, s), –0.01 (3H, s); \[ ^13C \text{ NMR} (100 MHz, CDCl₃) \]: δC 219.3, 139.3, 128.3, 128.3, 127.0, 127.0, 81.1, 78.6, 70.5, 58.8, 58.5, 56.3, 55.3, 49.7, 46.0, 25.9, 23.5, 18.2, 17.5, –4.0, –4.5; \[ \text{IR } \nu_{\text{max}} \]: 3309 (m, C≡C–H), 1745 (s, C=O); \[ \text{HRMS (ESI)} \]: [M + H]⁺ calcd. for C₂₄H₃₆NO₂Si⁺: 398.2510, found 398.2526.

Data of S5b:

\[ R_f = 0.35 \] (petroleum ether/EtOAc, 90:10); \[ ^1H \text{ NMR} (400 MHz, CDCl₃) \]: δH 7.37–7.21 (5H, m), 4.73 (1H, d, \( J = 6.3 \)), 3.69 (1H, d, \( J = 13.4 \)), 3.46 (1H, d, \( J = 13.4 \)), 3.19 (1H, d, \( J = 9.2 \)), 3.00 (2H, t, \( J = 9.2 \)), 2.90 (1H, d, \( J = 9.2 \)), 2.64–2.54 (2H, m), 2.31–2.23 (2H, m), 2.16 (1H, dd, \( J = 16.7, 2.6 \)), 2.38 (1H, dd, \( J = 8.9, 6.2 \)), 2.31–2.17 (2H, m), 1.96 (1H, t, \( J = 2.6 \)), 1.19 (3H, s), 0.94 (9H, s), 0.16 (3H, s), 0.13 (3H, s); \[ ^13C \text{ NMR} (100 MHz, CDCl₃) \]: δC 222.5, 139.0, 128.5, 128.3, 127.0, 81.4, 79.9, 70.4, 59.8, 58.3, 53.1, 53.0, 52.8, 43.4, 26.7, 25.9, 18.3, 18.2, –4.4, –4.8; \[ \text{IR } \nu_{\text{max}} \]: 3309 (m, C≡C–H), 1745 (s, C=O); \[ \text{HRMS (ESI)} \]: [M + H]⁺ calcd. for C₂₄H₃₆NO₂Si⁺: 398.2510, found 398.2528.
According to General Procedure D, S5a (22.0 mg, 55.3 µmol) and TBAF (1.0 M in THF, 0.111 mL, 0.111 mmol) gave a crude material. Purification via flash column chromatography (petroleum ether/EtOAc/Et3N, 65:35:1) gave 15a as a colourless amorphous solid (13.4 mg, 49.77 µmol, 90%). \( R_f = 0.25 \) (petroleum ether/EtOAc/Et3N, 65:35:1); \(^1\)H NMR (600 MHz, CDCl3): \( \delta \) 7.34–7.22 (5H, m), 4.12 (1H, d, \( J = 6.8 \)), 3.64 (1H, d, \( J = 13.2 \)), 3.52 (1H, d, \( J = 13.2 \)), 3.18 (1H, d, \( J = 9.1 \)), 3.05–3.00 (2H, m), 2.66 (1H, dt, \( J = 10.5, 6.8 \)), 2.46 (1H, dd, \( J = 17.1, 2.7 \)), 2.36 (1H, dd, \( J = 17.1, 2.7 \)), 2.30 (1H, dd, \( J = 9.4, 5.9 \)), 2.22 (1H, t, \( J = 9.1 \)), 2.11 (1H, t, \( J = 2.7 \)), 1.16 (3H, s); \(^13\)C NMR (151 MHz, CDCl3): \( \delta \)C 219.1, 138.9, 128.5, 128.4, 127.1, 81.4, 80.6, 71.3, 59.2, 58.8, 56.1, 53.4, 48.7, 44.7, 24.3, 16.1; IR \( v_{\text{max}} \): 3470 (br s, \( \text{O–H} \)), 3293 (m, \( \text{C≡C–H} \)), 1739 (s, \( \text{C=O} \)); HRMS (ESI): [M + H]\(^+\) calcd. for C18H22NO2+: 284.1645, found 284.1644.

According to General Procedure D, S5b (25.0 mg, 62.9 µmol) and TBAF (1.0 M in THF, 0.126 mL, 0.126 mmol) gave a crude material. Purification via flash column chromatography (petroleum ether/EtOAc/Et3N, 65:35:1) gave 15b as a (14.8 mg, 52.2 µmol, 83%). \( R_f = 0.25 \) (petroleum ether/EtOAc/Et3N, 65:35:1); \(^1\)H NMR (400 MHz, CDCl3): \( \delta \)H 7.39–7.22 (5H, m), 5.27 (1H, s), 4.15 (1H, d, \( J = 5.7 \)), 3.71 (1H, d, \( J = 12.8 \)), 3.60 (1H, d, \( J = 12.8 \)), 3.27 (1H, d, \( J = 9.5 \)), 3.19 (1H, d, \( J = 9.3 \)), 3.12 (1H, dt, \( J = 9.5, 5.7 \)), 3.00 (1H, dd, \( J = 10.6, 9.3 \)), 2.42–2.33 (2H, m), 2.29 (2H, t, \( J = 2.9 \)), 2.10 (1H, t, \( J = 2.9 \)), 1.27 (3H, s); \(^13\)C NMR (100 MHz, CDCl3): \( \delta \)C 219.8, 137.4, 128.7 (x 2), 127.7, 79.2, 76.2, 71.7, 59.2, 57.5, 55.5, 55.3, 48.0, 40.2, 25.4, 14.7; IR \( v_{\text{max}} \): 3297 (br s, O–H), 3280 (m, C≡C–H), 1739 (s, C=O); HRMS (ESI): [M + H]\(^+\) calcd. for C18H22NO2+: 284.1645, found 284.1644.

Allylmagnesium bromide (1.0 M in THF, 161 µL, 0.161 mmol) was added dropwise to stirred solution of anti-S1 (43.0 mg, 0.161 mmol) in anhydrous THF (3 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h, then concentrated in vacuo to give a mixture of diastereomers (75:25 dr). Purification via flash column
chromatography (petroleum ether/EtOAc, 97:3) gave 16 (30.3 mg, 0.100 mmol, 62%) as a single diastereomer. \( R_f = 0.26 \) (petroleum ether/EtOAc, 97:3); \(^1H\) NMR (400 MHz, CDCl\(_3\)):\( \delta \) 5.99 (1H, ddt, \( J = 17.4, 10.5, 7.1 \)), 5.12–5.07 (1H, m), 5.07–5.05 (1H, m), 4.30 (1H, d, \( J = 5.6 \)), 4.05 (1H, d, \( J = 1.9 \)), 2.29 (1H, dd, \( J = 13.7, 7.2 \)), 2.16 (1H, dd, \( J = 16.7, 2.7 \)), 2.06–1.95 (4H, m), 1.79–1.70 (1H, m), 1.17 (3H, s), 0.89 (9H, s), 0.08 (6H, s); \(^13C\) NMR (101 MHz, CDCl\(_3\)):\( \delta \) 134.9, 117.0, 83.8, 81.4, 81.3, 71.0, 51.8, 39.8, 36.3, 30.6, 25.9, 25.8, 18.0, 14.2, –4.7, –5.0; IR \( \nu_{\text{max}} \): 3511 (br, O–H), 3311 (s, C≡C–H), 1639 (s, C=C), 1462 (s, C=CH\(_2\)); HRMS (ESI): [M + H]\(^+\) calcd. for C\(_{18}\)H\(_{33}\)O\(_2\)Si: 309.2245, found 309.2241.

\((1R^*,3aR^*,7aS^*)\)-7a-Methyl-6-vinyl-1,2,3,4,7,7a-hexahydro-3aH-indene-1,3a-diol (17)

Grubbs 2\(^{nd}\) generation catalyst (10.7 mg, 12.6 µmol) was added to a stirred solution of 16 (39.0 mg, 0.126 mmol) in anhydrous CH\(_2\)Cl\(_2\) (25 mL). The reaction mixture was stirred under an ethylene atmosphere at rt for 4 h then concentrated in vacuo. TBAF (1.0 M in THF, 0.253 mL, 0.253 mmol) was added to a solution of the crude product in anhydrous THF (3 mL). The solution was stirred at rt for 2 h, then concentrated in vacuo. Purification via flash column chromatography (petroleum ether/EtOAc, 60:40) gave 17 as a white amorphous solid (16.0 mg, 82.8 µmol, 66%); \( R_f = 0.35 \) (petroleum ether/EtOAc, 60:40); \(^1H\) NMR (600 MHz, CDCl\(_3\)):\( \delta \) 6.36 (1H, dd, \( J = 17.5, 10.8 \)), 5.60 (1H, dt, \( J = 5.4, 2.6 \)), 5.01 (1H, d, \( J = 17.5 \)), 4.92 (1H, t, \( J = 6.3 \)), 3.89 (1H, t, \( J = 6.3 \)), 2.58 (1H, d, \( J = 7.2 \)), 2.53 (1H, s), 2.45 (1H, ddd, \( J = 18.8, 5.4, 2.1 \)), 2.40–2.29 (1H, m), 2.26 (1H, d, \( J = 18.8 \)), 2.05 (1H, d, \( J = 17.6 \)), 1.87–1.78 (3H, m), 1.69 (1H, d, \( J = 17.6 \)), 1.07 (3H, s); \(^13C\) NMR (151 MHz, CDCl\(_3\)):\( \delta \) 139.4, 133.2, 126.2, 110.9, 82.0, 81.9, 46.5, 36.1, 34.8, 34.5, 31.3, 14.7; IR \( \nu_{\text{max}} \): 3353 (br., O–H), 1647 (m, C=C), 1607 (m, C=C), 1607 (m, C=C), 1460 (s, C=CH\(_2\)); HRMS (ESI): [M – H]\(^–\) calcd. for C\(_{12}\)H\(_{17}\)O\(_2\): 193.1234, found 193.1229.

\((4aS^*,5R^*,7aR^*,8aR^*)\)-5,7a-Di-hydroxy-4a-methyl-4,4a,5,6,7,7a,8,8a-octahydro-s-indacen-2(1H)-one (18a) and \((4aS^*,5R^*,7aR^*,8aS^*)\)-5,7a-di-hydroxy-4a-methyl-4,4a,5,6,7,7a,8,8a-octahydro-s-indacen-2(1H)-one (18b)

A solution of Co\(_2\)(CO)\(_8\) (68.0 mg, 0.195 mmol) in anhydrous CH\(_2\)Cl\(_2\) (5 mL) was added to a stirred solution of 16 (50.0 mg, 0.162 mmol) in anhydrous CH\(_2\)Cl\(_2\) (1 mL) at rt. The reaction mixture was stirred at rt for 2 h, then 4-methylmorpholine \( N \)-oxide (190 mg, 1.62 mmol) was added portion-wise and the mixture was stirred for a further 18 h. The violet Co precipitate was removed by filtration through a short plug of silica (washed with CH\(_2\)Cl\(_2\)/MeOH 19:1) and the filtrate was concentrated in vacuo. TBAF (1.0 M in THF, 0.325 mL, 0.324 mmol) was added to a solution of the crude product in anhydrous THF (3.5 mL). The solution was stirred at rt for 1 h, then concentrated in vacuo to give a mixture of diastereomers (71:29 \( dr \)). Purification via flash column chromatography (petroleum ether/EtOAc, 7:3) gave 18a (16.1 mg, 0.065 mmol, 40%) and 18b (16.5 mg, 0.068 mmol, 42%) as a single diastereomer.
chromatography (EtOAc) gave 18a (15.0 mg, 67.6 µmol, 42%) and 18b (6.0 mg, 27.0 µmol, 17%) both as colourless oils.

Data of 18a:

Rf = 0.29 (EtOAc); 1H NMR (600 MHz, CDCl3): δH 5.93 (1H, t, J 1.8), 3.88 (1H, t, J 6.6), 2.81 (1H, dtt, J 12.8, 6.4, 1.8), 2.74 (1H, s), 2.65–2.58 (2H, m), 2.43 (1H, d, J 13.8), 2.40–2.32 (1H, m), 2.29–2.20 (2H, m), 2.07 (1H, ddd, J 18.7, 2.4, 0.9), 2.04–1.93 (3H, m), 1.38 (1H, t, J 12.8), 1.03 (3H, s); 13C NMR (151 MHz, CDCl3) δC 208.5, 180.0, 130.1, 82.6, 82.3, 51.1, 42.2, 39.8, 38.7, 38.6, 34.9, 31.1, 14.2; IR vmax: 3385 (br., O–H), 1704 (s, C=O), 1620 (s, C=C); HRMS (ESI): [M + H]+ calcd. for C13H19O3+: 223.1329, found 223.1341.

Data of 18b:

Rf = 0.28 (EtOAc); 1H NMR (400 MHz, CDCl3): δH 5.93 (1H, t, J 1.8), 3.88 (1H, q, J 8.0), 3.01 (1H, dt, J 14.6, 6.6, 0.7), 2.78 (1H, m), 2.65 (6H s), 2.33 (3H, s); 13C NMR (101 MHz, CDCl3) δC 208.8, 181.7, 128.9, 78.1, 73.6, 49.4, 44.3, 41.8, 37.1, 36.1, 34.9, 28.5, 15.8; IR vmax: 3391 (br, O–H), 1704 (s, C=O), 1618 (s, C=C); HRMS (ESI): [M + H]+ calcd. for C13H19O3+: 223.1329, found 223.1341.

O-Mesitylsulfonylhydroxylamine (S6)

Et3N (1.5 mL, 10.8 mmol) was added to a stirred solution of Ethyl N-hydroxyacetamidate (1.18 g, 11.4 mmol) in DMF (6 mL) and the solution was cooled to 0 °C. 2-Mesitylsulfonylchloride (2.5 g, 11.4 mmol) was added in small portions and the mixture was stirred vigorously for 30 min. The reaction was diluted with Et2O (100 mL) and washed with H2O (5 × 50 mL). The organic layer was dried and concentrated in vacuo. Ethyl-O-(mesitylsulfonyl)acetohydroxamate (2.20 g) was obtained and used in the next step without further purification.

Perchloric acid (70%, 0.95 mL) was added dropwise to a stirred solution of Ethyl-O-(mesitylsulfonyl)-acetohydroxamate (2.20 g, 7.72 mmol) in dioxane (3 mL) at 0 °C. The reaction was stirred for 10 min, then transferred onto ice water (100 mL). The aqueous layer was extracted with Et2O (3 × 30 mL) and the combined organic layers were washed with brine (2 × 50 mL) then dried/neutralized with K2CO3. After filtration, the solution was concentrated to a volume less than 10 mL and poured into 20 mL of ice-cold petroleum ether. After crystallization, S6 was obtained (805 mg, 4.04 mmol, 37%) as a white crystalline solid. RI = 0.32 (elucent hexane/EtOAc, 80:20); m.p. 93 °C [Lit. 90-91 °C].1 1H NMR (400 MHz, CDCl3): δH 7.00 (2H, s), 2.65 (6H s), 2.33 (3H, s); 13C NMR (101 MHz, CDCl3): δC 143.9, 141.1, 131.9, 129.3, 22.9, 21.2; IR vmax: 3469, 3198 (m, N–H stretch), 2980 (br, Ar C–H), 1603 (s, N–H bend), 1170 (s, S=O). These characterisation data are in accordance with that previously reported in the literature.2
(5R*,6S*)-5-((tert-Butyldimethylsilyl)oxy)-6-methyl-6-(prop-2-yn-1-yl)piperidin-2-one (19)

![Chemical Structure](image)

S6 (636 mg, 2.95 mmol) was added to a stirred solution of anti-S1 (432 mg, 1.62 mmol) in CH₂Cl₂ (5 ml) at 0 °C. After 20 min the temperature was raised to rt and the solution was stirred for a further 18 h. BF₃·Et₂O (0.63 ml, 5.1 mmol) was added, and the mixture was stirred at rt for 1 h. The reaction mixture was diluted with CH₂Cl₂ (50 ml) and washed with saturated aqueous NaHCO₃ (2 × 50 ml). The aqueous layers were re-extracted with Et₂O (3 × 50 ml), and the combined organic layers were dried and concentrated in vacuo. Purification via flash column chromatography (hexane/EtOAc, 50:50) gave 19 as a white crystalline solid (300 mg, 1.07 mmol, 66%); R_f = 0.20 (hexane/EtOAc, 50:50); m.p. 125 ºC; ¹H NMR (400 MHz, CDCl₃): δH 5.95 (1H, br s), 3.84 (1H, dd, J 7.8, 4.9), 2.58–2.26 (4H, m), 2.11 (1H, t, J 2.7), 1.90 (2H, td, J 8.0, 5.1), 1.28 (3H, s), 0.89 (9H, s), 0.09 (6H, s); ¹³C NMR (101 MHz, CDCl₃): δC 171.0, 79.3, 72.6, 70.7, 58.0, 31.7, 28.3, 25.8, 22.3, 18.1, ~4.1, ~4.9; IR ν_max: 3313 (s, C≡C–H), 1660 (s, C=O); HRMS (ESI): [M+H]^+: 282.1884, found: 282.1879.

(5R*,6S*)-5-Hydroxy-6-methyl-6-(prop-2-yn-1-yl)piperidin-2-one (20)

According to General Procedure D, 19 (30 mg, 0.11 mmol) and TBAF (1.0 M in THF, 0.168 mL, 0.168 mmol) gave a crude material. Purification via flash column chromatography (EtOAc/MeOH, 95:5) gave 20 as a colourless oil (17 mg, 0.10 mmol, 94%). R_f = 0.21 (EtOAc/MeOH, 95:5); ¹H NMR (400 MHz, CDCl₃): δH 5.95 (1H, br s), 3.88 (1H, td, J 6.6, 3.4), 2.59–2.25 (6H, m), 2.14 (1H, t, J 2.7), 2.06–1.91 (2H, m), 1.34 (3H, s); ¹³C NMR (101 MHz, CDCl₃): δC 171.0, 79.1, 72.8, 70.4, 57.5, 31.8, 28.3, 25.6, 21.7; IR ν_max: 3305 (m, N–H), 1638 (s, C=O); HRMS (ESI): [M+H]^+: 168.1019, found 168.1018.
(5R*,6S*)-1-Allyl-5-[(tert-butyldimethylsilyl)oxy]-6-methyl-6-(prop-2-yn-1-yl)piperidin-2-one (S7)

NaH (60% in mineral oil, 33 mg, 0.22 mmol) was added to a stirred solution of 19 (190 mg, 0.66 mmol) in anhydrous DMF (7 mL) at 0 °C. The mixture was stirred at rt for 30 min, then allyl bromide (0.126 mL, 1.46 mmol) was added and the reaction mixture was stirred for another 2 h. The mixture was diluted with EtOAc (200 mL), washed with H2O (2 × 150 mL) and brine (1 × 150 mL), and the organic extract was dried and concentrated in vacuo. Purification via flash column chromatography (petroleum ether/EtOAc, 80:20) gave S7 as a colourless oil (161 mg, 0.50 mmol, 76%).

Rf = 0.19 (petroleum ether/EtOAc, 80:20); 1H NMR (400 MHz, CDCl3): δ 5.88 (1H, ddd, J 17.3, 10.3, 5.9, 5.0), 5.19–5.05 (2H, m), 4.26 (1H, ddt, J 16.1, 5.1, 1.8), 4.09 (1H, dd, J 8.2, 3.0), 2.66–2.55 (2H, m), 2.48–2.34 (2H, m), 2.06 (1H, t, J 2.7), 1.95 (1H, dd, J 13.8, 6.9, 3.0), 1.83 (1H, ddd, J 13.7, 8.2, 6.7), 1.29 (3H, s), 0.90 (9H, s), 0.12 (3H, s), 0.11 (3H, s); 13C NMR (151 MHz, CDCl3): δc 170.0, 135.7, 115.8, 79.8, 72.3, 70.3, 63.6, 45.0, 28.8, 28.7, 25.9, 24.9, 21.7, 18.1, –4.1, –4.9; IR νmax: 3314 (s, C≡C–H), 1639 (m, C=O); HRMS (ESI): [M + H]+ calcd. for C18H32NO2Si+: 322.2197, found 322.2198.

(3aR*,9R*,9aS*)-9-Hydroxy-9a-methyl-3a,4,8,9,9a,10-hexahydrocyclopenta[b]quinolizine-2,6(3H,7H)-dione (21)

S7 (38.0 mg, 0.118 mmol) in CH2Cl2 (1.0 mL) was added to a stirred solution of Co2(CO)8 (50.5 mg, 0.147 mmol) in CH2Cl2 (4.25 mL) at rt. The reaction mixture was stirred at rt for 2 h, then 4-methylmorpholine N-oxide (138 mg, 1.18 mmol) was added portion-wise and the mixture was stirred for a further 18 h. The violet Co precipitate was removed by filtration through a short plug of silica (washed with CH2Cl2/MeOH 19:1) and the filtrate was concentrated in vacuo. TBAF (1.0 M in THF, 0.21 mL, 0.21 mmol) was added to a solution of the crude product in anhydrous THF (5.4 mL). The solution was stirred at rt for 2 h, then concentrated in vacuo. Purification via flash column chromatography (EtOAc/MeOH, 95:5) gave 21 as a colourless oil (21.1 mg, 89.8 μmol, 76%).

Rf = 0.34 (EtOAc/MeOH, 90:10); 1H NMR (400 MHz, CD3OD): δ 6.02 (1H, d, J 1.8), 5.05 (1H, dd, J 13.2, 6.6), 3.89 (1H, app p, J 7.5), 3.03 (1H, d, J 13.5), 2.78 (1H, dt, J 13.0, 6.7), 2.73–2.37 (5H, m), 2.10–2.02 (1H, m), 1.98 (2H, tt, J 8.5, 4.7), 1.24 (3H, s); 13C NMR (101 MHz, CD3OD): δc 207.6, 177.5, 169.1, 130.1, 74.0, 61.2, 43.9, 41.9, 40.2, 39.0, 29.8, 25.5, 17.8; IR νmax: 3361 (br., O–H), 1702 (s, C=O), 1673 (s, C=O), 1614 (s, C=C), 1407 (s, O–H); HRMS (ESI): [M + H]+ calcd. for C13H18NO3Si+: 236.1283, found 236.1283.
Grubbs 2nd generation catalyst (12.0 mg, 0.142 µmol) was added to a stirred solution of S7 (40 mg, 0.142 mmol) in anhydrous CH$_2$Cl$_2$ (25 mL). The reaction mixture was stirred under an ethylene atmosphere at rt for 4 h then concentrated in vacuo. TBAF (1.0 M in THF, 0.253 mL, 0.253 mmol) was added to a solution of the crude product in anhydrous THF (3 mL). The solution was stirred at rt for 2 h, then concentrated in vacuo. Purification via flash column chromatography (eluent EtOAc/MeOH, 98:2) gave 22 as a white amorphous solid (20.0 mg, 0.097 mmol, 69%). R$_f$ = 0.39 (EtOAc/MeOH, 9:1); $^1$H NMR (400 MHz, CD$_3$OD): δ $H$ 6.49 (1H, dd, J $= 17.5$, 10.8), 5.79 (1H, q, J $= 3.2$), 5.22 (1H, d, J $= 17.5$), 5.06 (1H, dt, J $= 20.5$, 3.6), 3.83 (1H, t, J $= 6.7$), 3.68–3.57 (1H, m), 2.63–2.53 (2H, m), 2.53–2.42 (1H, m), 2.21 (1H, dd, J $= 16.7$, 3.1), 2.07–1.87 (2H, m), 1.28 (3H, s); $^{13}$C NMR (101 MHz, CD$_3$OD): δ $C$ 171.8, 139.6, 133.7, 124.0, 112.4, 73.9, 59.8, 41.5, 36.7, 30.3, 25.6, 18.6; IR $\nu_{max}$: 3370 (br., O–H), 1611 (s, C=O), 1600 (s, C=C), 1408 (s, O–H); HRMS (ESI): [M + H]$^+$ calcd. for C$_{12}$H$_{18}$NO$_2$ 208.1332, found 208.1328.

Anti-8-((tert-Butyldimethylsilyl)oxy)-8a-methyl-6,7,8,8a-tetrahydroindolizin-5(1H)-one (S8)

InCl$_3$ (101 mg, 0.46 mmol) was introduced into 10 mL flask and heated with a heat gun (150 °C) under vacuum for 2 min. After being allowed to cool to room temperature, THF (1.2 mL) was added. The mixture was stirred at room temperature for 10 min and then cooled to –78 °C. DIBAL-H (1.0 M in hexane, 0.44 mL, 0.44 mmol) was added dropwise and the mixture was stirred at –78 °C for 40 min. 19 (83 mg, 0.30 mmol) was then added, followed by Et$_3$B (1.0 M in THF, 0.17 mL, 0.17 mmol) and the mixture was stirred at –78 °C for 4 hours. A solution of iodine (449 mg, 1.78 mmol) in THF (0.75 mL) was then added. After 40 minutes, the mixture was poured onto satd. NaHCO$_3$ (5 mL). Na$_2$S$_2$O$_3$ was added under stirring until complete decoloration and the aqueous layer was extracted with EtOAc (5 × 10 mL). The combined organic layers were washed with brine (50 mL), dried and concentrated in vacuo.

Cs$_2$CO$_3$ (115 mg, 0.35 mmol), Cul (23 mg, 0.12 mmol) and N$_2$N'-dimethyl-1,2-diamine (25 µL, 0.24 mmol) were added to a stirred solution of the crude product in PhMe (2 mL) and the mixture was heated to 85 °C for 3 hours. H$_2$O (10 mL) was added and the reaction extracted with CH$_2$Cl$_2$ (5 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried and concentrated in vacuo. Purification via flash column chromatography (Petroleum ether/EtOAc, 60:40) gave S8 as a white amorphous solid (53 mg, 0.19 mmol, 64%). R$_f$ = 0.32 (Petroleum ether/EtOAc, 50:50); $^1$H NMR (400 MHz, CDCl$_3$): δ $H$ 6.81 (1H, t, J $= 4.1$), 5.19 (1H, dt, J $= 4.8$, 2.6), 3.85 (1H, t, J $= 8.4$), 2.70–2.51 (2H, m), 2.51–2.32 (2H, m), 1.87 (2H, td, J $= 7.9$, 7.1, 5.3), 1.23 (3H, s), 0.87 (9H, s), 0.06 (6H, 2 ×
s; $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$C 165.5, 128.0, 110.3, 73.4, 65.3, 44.8, 29.1, 26.5, 25.7, 19.5, 18.0, −3.9, −4.8; IR $\nu_{\text{max}}$: 1664 (s, C=O), 1629 (s, C=C); HRMS (ESI): [M+H]$^+$ calcd. for C$_{15}$H$_{28}$NO$_2$: 282.1884, found: 282.1882.

(8R*,8aS*)-8-Hydroxy-8a-methyl-6,7,8,8a-tetrahydroindolizin-5(1H)-one (23)

According to General Procedure D, S8 (53 mg, 0.19 mmol) and TBAF (1.0 M in THF, 0.27 mL, 0.27 mmol) gave a crude material. Purification via flash column chromatography (EtOAc/MeOH, 95:5) gave 23 as a colourless oil (25 mg, 0.15 mmol, 79%). $R_f = 0.36$ (EtOAc/MeOH, 95:5); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$H 6.80 (1H, ddd, $J$ 4.4, 2.9, 1.4), 5.28–5.21 (1H, m), 3.88 (1H, dd, $J$ 11.6, 5.4), 2.78 (1H, dt, $J$ 16.3, 2.5), 2.58 (1H, ddd, $J$ 18.9, 9.3, 2.3), 2.52–2.41 (2H, m), 2.04–1.83 (2H, m), 1.25 (3H, s); $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$C 165.8, 127.8, 111.0, 72.4, 65.1, 44.3, 29.1, 25.8, 19.2; IR $\nu_{\text{max}}$: 1603 (m, C=O), 1440 (m, O-H); HRMS (ESI): [M+H]$^+$ calcd. for C$_9$H$_{14}$NO$_2$: 168.1019, found: 168.1025.

(2S*,3R*)-3-((tert-Butyldimethylsilyl)oxy)-2-methyl-2-((3-phenyloxazol-4-yl)methyl)cyclopentan-1-one (S9)

Cp*Ru(COD)Cl (10 mg, 0.028 mmol) and NEt$_3$ (80 $\mu$L, 0.57 mmol) were added to a degassed solution of α-chlorobenzaldoxime (200 mg, 1.3 mmol) and anti-S1 (69 mg, 0.26 mmol) in DCE (5 mL). The mixture was stirred at 80 °C for 24 h before being concentrated in vacuo. Purification via flash column chromatography (eluent hexane/EtOAc, 93:7) gave S9 (77 mg, 0.20 mmol, 77%) as a colourless oil. $R_f = 0.28$ (eluent hexane/EtOAc, 90:10); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$H 8.29 (1H, app s), 7.56–7.46 (5H, m), 3.87 (1H, t, $J$ 5.8), 2.69 (1H, d, $J$ 15.1), 2.58 (1H, d, $J$ 15.1), 2.39 (1H, ddd, $J$ 18.8, 9.6, 5.7), 1.98 (1H, ddd, $J$ 18.8, 9.0, 7.2), 1.87 (1H, app ddt, $J$ 12.9, 9.0, 5.7), 1.68 (ddddd, $J$ 12.9, 9.6, 7.2, 5.8), 0.90 (3H, s), 0.75 (9H, s), −0.08 (3H, s), −0.20 (3H, s); $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$C 220.4, 162.7, 157.7, 129.6, 129.1, 129.0, 128.9, 113.6, 75.3, 54.4, 35.1, 28.4, 27.0, 25.7, 18.0, 16.3, −4.3, −5.1; IR $\nu_{\text{max}}$: 3619 (br, O–H), 1739 (s, C=O); HRMS (ESI): [M+H]$^+$ calcd. for C$_{22}$H$_{32}$O$_3$NSi$: 386.2146, found: 386.2154.
TBAF (1.0 M in THF, 2.0 mL, 2.0 mmol) was added to a stirred solution of S9 (76 mg, 0.20 mmol) and AcOH (0.20 mL) in THF (7.8 mL) under argon. The reaction mixture was stirred at rt for 5 days, then concentrated in vacuo. The residue was treated with brine (4 mL) and satd. NaHCO₃ to adjust the pH to 7. The aqueous layer was extracted with Et₂O (3 × 10 mL), and the combined extracts were dried and concentrated in vacuo. Purification via flash column chromatography (petroleum ether/EtOAc, 55:45) gave 24 as a yellow oil (43 mg, 0.16 mmol, 80%). Rf = 0.24 (petroleum ether/EtOAc, 50:50); ¹H NMR (400 MHz, CDCl₃): δH 8.22 (1H, s), 7.58 (2H, dd, J 6.7, 3.0), 7.53–7.43 (3H, m), 3.82 (1H, dd, J 8.8, 6.5), 2.86 (1H, d, J 5.1), 2.65 (1H, d, J 15.1), 2.40 (1H, ddd, J 19.2, 9.3, 2.7), 2.00 (1H, dddd, J 11.9, 9.0, 6.3, 2.6), 1.89 (1H, dt, J 19.0, 9.3), 1.71 (1H, dq, J 12.0, 9.2), 1.37 (1H, br s), 0.93 (3H, s); ¹³C NMR (101 MHz, CDCl₃): δC 219.2, 162.7, 158.0, 129.9, 129.2, 129.0, 128.8, 113.8, 73.4, 54.4, 35.5, 27.3, 26.3, 16.0; IR νmax: 3422 (br, O–H), 1732 (s, C=O); HRMS (ESI): [M+H]+ calcd. for C₁₆H₁₈NO₃+: 272.1281, found: 272.1281.

**Ethyl 2-[[1(S*,2S*)-2-((tert-butyldimethylsilyl)oxy)-1-methyl-5-oxocyclopentyl)methyl]-1H-1,2,3-triazol-1-yl]acetate (S10)**

[Cp*RuCl]₄ (59 mg, 0.054 mmol) was added to a degassed solution of syn-S1 (130 mg, 0.49 mmol) and ethyl azidoacetate (114 mg, 0.88 mmol) in PhMe (8 mL) under argon. The reaction mixture was stirred at rt for 18 hours before being concentrated in vacuo. Purification via flash column chromatography (hexane/EtOAc, 60:40) gave S10 as a yellow oil (160 mg, 0.42 mmol, 86%). Rf = 0.26 (hexane/EtOAc, 60:40); ¹H NMR (400 MHz, CDCl₃): δH 7.52 (1H, s), 5.19 (1H, d, J 17.7), 5.12 (1H, d, J 17.7), 4.27–4.16 (3H, m), 2.79 (2H, app s), 2.41–2.22 (2H, m), 2.15 (1H, m), 1.78 (1H, m), 1.27 (3H, t, J 7.1), 0.98 (3H, s), 0.84 (9H, s), 0.11 (3H, s), 0.03 (3H, s); ¹³C NMR (101 MHz, CDCl₃): δC 219.6, 166.6, 134.9, 133.7, 78.1, 62.5, 53.7, 49.1, 33.9, 28.4, 25.9, 24.6, 20.0, 18.2, 14.3, –4.0, –4.8; IR νmax: 1743 (s, C=O); HRMS (ESI): [M+H]+ calcd. for C₁₉H₂₄N₅O₅Si+: 396.2313, found: 396.2313.
Ethyl 2-((5-(((1R*,2S*)-2-hydroxy-1-methyl-5-oxocyclopentyl)methyl)-1H-1,2,3-triazol-1-yl)acetate (25)

TBAF (3.3 mL, 1 M in THF, 3.3 mmol) was added to a stirred solution of S10 (125 mg, 0.32 mmol) and AcOH (0.33 mL, 5.7 mmol) in THF (12.5 mL) under argon. The reaction mixture was stirred at rt for 5 days, then concentrated in vacuo. The residue was treated with brine (4 mL) and satd. NaHCO₃ to adjust the pH to 7. The aqueous layer was extracted with Et₂O (3 × 10 mL), and the combined extracts were dried and concentrated in vacuo. Purification via flash column chromatography (eluent hexane/EtOAc, 70:30) gave 25 as a yellow oil (67 mg, 0.24 mmol, 76%). Rf = 0.09 (eluent hexane/EtOAc, 60:40); ¹H NMR (400 MHz, CDCl₃): δH 7.55 (1H, s), 5.30 (1H, d, J 17.6), 5.15 (1H, d, J 17.6), 4.22 (2H, q, J 7.1), 4.06 (1H, dd, J 4.1, 1.7), 2.93 (1H, d, J 15.6), 2.79 (1H, d, J 15.6), 2.50–2.34 (2H, m), 2.27–2.13 (1H, m), 1.97–1.88 (1H, m), 1.26 (3H, t, J 7.1), 1.00 (3H, s); ¹³C NMR (101 MHz, CDCl₃): δC 220.1, 166.9, 135.4, 133.5, 75.5, 62.3, 53.7, 49.0, 33.4, 28.3, 19.8, 14.0; IR νmax: 3338 (br, O–H), 1741 (s, C=O); HRMS (ESI): [M+H]+ calcd. for C₁₃H₂₀N₃O₄+: 282.1448, found: 282.1445.

(1R*,2S*)-2-Methyl-3-oxo-2-(prop-2-yn-1-yl)cyclopentane-1-carbonitrile (anti-26)

MsCl (76 µL, 0.99 mmol) was added to a stirred solution of anti-1 (50 mg, 0.33 mmol) in pyridine (2.25 mL) at 0 °C, and the resultant mixture was stirred at rt for 24 h. After addition of 1 M HCl (20 mL), the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried and concentrated in vacuo. KCN (42 mg, 0.64 mmol) was added to a stirred solution of the crude material in DMSO (3 mL) at rt, and the resultant mixture was stirred for 5 days. After addition of aq. NaCl (20 mL), the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried and concentrated in vacuo. Purification via flash column chromatography (eluent hexane/EtOAc, 85:15) gave anti-26 as an amorphous white solid (38 mg, 0.24 mmol, 72%). Rf = 0.16 (eluent hexane/EtOAc, 85:15); ¹H NMR (400 MHz, CDCl₃): δH 3.47 (1H, dd, J 11.0, 6.8), 2.63–2.52 (2H, m), 2.52–2.32 (1H, m), 2.36 (1H, dd, J 17.0, 2.7), 2.29–2.09 (2H, m), 2.07 (1H, t, J 2.7), 1.22 (3H, s); ¹³C NMR (101 MHz, CDCl₃): δC 214.7, 119.0, 79.2, 72.5, 50.7, 36.2, 34.9, 25.7, 23.5, 19.5; IR νmax: 3291 (C≡C–H), 2242 (m, C≡N), 1746 (s, C=O); HRMS (ESI): [M+H]+ calcd. for C₁₀H₁₂N₂O+: 162.0913, found: 162.0914.
(1S*,25*)-2-Methyl-3-oxo-2-(prop-2-yn-1-yl)cyclopentane-1-carbonitrile (syn-26)

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\text{syn-26}
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MsCl (95 µL, 1.23 mmol) was added to a stirred solution of syn-1 (63 mg, 0.41 mmol) in pyridine (2.80 mL) at 0 °C, and the resultant mixture was stirred at rt for 24 h. After addition of 1 M HCl (20 mL), the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried and concentrated in vacuo. The crude mesylate was used in the next step without further purification. KCN (50 mg, 0.77 mmol) was added to a stirred solution of the crude material in DMSO (3.5 mL) at rt, and the resultant mixture was stirred for 5 days. After addition of aq. NaCl (20 mL), the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried and concentrated in vacuo. Purification via flash column chromatography (eluent hexane/EtOAc, 80:20) gave syn-26 as an amorphous white solid (40 mg, 0.25 mmol, 60%). \( R_f = 0.19 \) (eluent hexane/EtOAc, 80:20); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \)H 3.10–3.05 (1H, m), 2.65–2.27 (6H, m), 2.09 (1H, t, \( J \) 2.7), 1.24 (3H, s); \(^13\)C NMR (101 MHz, CDCl\(_3\)): \( \delta \)C 215.2, 119.1, 78.8, 71.9, 50.6, 37.9, 35.5, 24.9, 23.6, 21.6; IR \( v_{\text{max}} \): 3291 (s, C≡C–H), 2242 (m, C≡N), 1744 (s, C=O); HRMS (ESI): [M+H]\(^+\) calcd. for C\(_{10}\)H\(_{12}\)NO+: 162.0913, found: 162.0914.

Ethyl (5aS*,8aS*)-5a-methyl-6-oxo-5,5a,6,7,8,8a-hexahydropentaleno[1,2-b]pyridine-2-carboxylate (27)

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CpCo(CO)\(_2\) (11 mg, 60 µmol) was added to a degassed solution of syn-26 (20 mg, 120 µmol) and ethyl propiolate (62 µL, 600 µmol) in PhMe (1 mL) in a vial. The vial was sealed and the reaction mixture was stirred at 110 °C for 18 h. Upon completion, the reaction mixture was filtered through celite, washed with EtOAc (20 mL) and the filtrate concentrated in vacuo. Purification via flash column chromatography (hexane/EtOAc, 70:30) gave 27 as a yellow oil (3 mg, 0.012 mmol, 10%). \( R_f = 0.21 \) (hexane/EtOAc, 75:35); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \)H 7.94 (1H, d, \( J \) 7.9), 7.55 (1H, d, \( J \) 7.9), 4.56–4.40 (2H, m), 3.66 (1H, d, \( J \) 6.7), 3.29 (1H, d, \( J \) 17.3), 2.88 (1H, d, \( J \) 17.3), 2.71–2.58 (1H, m), 2.49–2.30 (2H, m), 2.00–1.85 (1H, m), 1.44 (3H, t, \( J \) 7.1), 1.34 (3H, s); \(^13\)C NMR (101 MHz, CDCl\(_3\)): \( \delta \)C 223.7, 165.7, 165.5, 148.0, 140.1, 132.9 124.1, 62.0, 54.8, 54.4, 40.6, 36.6, 23.9, 21.2, 14.5; IR \( v_{\text{max}} \): 1735 (m, C=O), 1447, 1410 (C=C); HRMS (ESI): [M+H]\(^+\) calcd. for C\(_{15}\)H\(_{18}\)NO\(_3\): 260.1281, found: 260.1280.

Ethyl (E)-3-(((1S*,2S*)-2-methyl-3-oxo-2-(prop-2-yn-1-yl)cyclopentyl)oxy)acrylate (28)

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Ethyl propiolate (30 µL, 0.3 mmol) and NMM (30 mg, 0.3 mmol) were added to a stirred solution of syn-1 (100 mg, 0.66 mmol) in CH\(_2\)Cl\(_2\) (2 mL). The mixture was stirred at rt for 2 h then concentrated in vacuo. Purification via
flash column chromatography (hexane/EtOAc, 82:18) gave 28 as a colourless oil (153 mg, 0.61 mmol, 93%). \( R_f = 0.10 \) (hexane/EtOAc, 90:10); \(^1H\) NMR (400 MHz, CDCl\(_3\)): \( \delta \) \( H \) 7.54 (1H, d, \( J \) 12.5), 5.29 (1H, d, \( J \) 12.5), 4.43 (1H, t, \( J \) 2.8), 4.17 (2H, q, \( J \) 7.1), 2.90–2.35 (4H, m), 1.98 (1H, t, \( J \) 2.7), 1.27 (3H, t, \( J \) 7.1), 1.19 (3H, s); \(^{13}C\) NMR (100 MHz, CDCl\(_3\)): \( \delta \) \( C \) 217.1, 167.8, 161.0, 98.6, 86.1, 80.3, 70.7, 60.1, 52.8, 33.7, 24.8, 20.8, 20.0, 14.5; IR \( \nu_{\text{max}} \): 1743 (s, C=O ketone), 1705 (s, C=O ester), 1643 (m, C=C), 1622 (m, C=C); HRMS (ESI): [M+H]\(^+\) calcd. for \( C_{14}H_{19}O_4 \): 251.1283, found: 251.1279.

Ethyl 2-((2\( R^*,\)4a\( S^*,\)7a\( S^*\)*)-4a-methyl-3-methylene-5-oxooctahydrocyclopenta[b]pyran-2-yl)acetate (29)

A degassed solution of Bu\(_3\)SnH (0.08 mL, 0.29 mmol) and AIBN (5.9 mg, 36.0 \( \mu \)mol) in PhMe (0.72 mL) was added dropwise over 5 h to a degassed solution of 28 (36 mg, 0.144 mmol) in PhMe (2.16 mL) at 80 °C. The reaction mixture was stirred for a further 12 h at 80 °C, then concentrated in vacuo. \( p \)-Toluenesulfonic acid monohydrate (15 mg, 76.5 \( \mu \)mol) was added to a stirred solution of the crude material in CH\(_2\)Cl\(_2\) (0.3 mL) at rt. The mixture was stirred for 1.5 h, then poured into satd. NaHCO\(_3\) (5 mL) and extracted with CH\(_2\)Cl\(_2\) (3 × 5 mL). The combined organic extracts were dried and concentrated in vacuo. Purification via flash column chromatography (hexane/EtOAc, 90:10) gave 29 as a colourless oil (21.4 mg, 85.0 \( \mu \)mol, 59%). \( R_f = 0.18 \) (hexane/EtOAc, 90:10); \(^1H\) NMR (400 MHz, CDCl\(_3\)): \( \delta \) \( H \) 4.87 (1H, d, \( J \) 1.7), 4.74 (d, \( J \) 1.6), 4.26 (1H, dd, \( J \) 8.2, 5.2), 4.16 (2H, qq, \( J \) 7.5, 3.7), 3.95 (1H, d, \( J \) 4.0), 2.70 (1H, d, \( J \) 14.0), 2.67–2.48 (2H, m), 2.47–2.24 (2H, m), 2.20–1.96 (3H, m), 1.26 (3H, t, \( J \) 7.1), 0.96 (3H, s); \(^{13}C\) NMR (100 MHz, CDCl\(_3\)): \( \delta \) \( C \) 220.0, 171.4, 142.8, 108.9, 83.1, 74.2, 60.7, 51.5, 38.2, 37.8, 34.0, 25.7, 21.2, 14.3; IR \( \nu_{\text{max}} \): 1708 (br, C=O ketone); HRMS (ESI): [M+H]\(^+\) calcd. for \( C_{14}H_{20}O_4Na \): 275.1254, found: 275.1249.

(15\( S^*,\)25\( S^*\)))-2-Methyl-3-oxo-2-(prop-2-yn-1-yl)cyclopentyl hex-5-enoate (30)

According to General Procedure F, \( \text{syn-1} \) (100 mg, 0.66 mmol), 5-hexenoic acid (0.11 mL, 0.891 mmol), DMAP (8 mg, 0.066 mmol) and DCC (184 mg, 0.891 mmol) gave a crude material. Purification via flash column chromatography (petroleum ether/EtOAc, 88:12) gave 30 as a colourless oil (149 mg, 0.60 mmol, 91%). \( R_f = 0.11 \) (eluent petroleum ether/EtOAc, 92:8); \(^1H\) NMR (400 MHz, CDCl\(_3\)): \( \delta \) \( H \) 5.77 (1H, ddt, \( J \) 17.0, 10.2, 6.7), 5.25 (1H, dd, \( J \) 4.6, 1.8), 5.08–4.95 (2H, m), 2.48–2.36 (4H, m), 2.36–2.22 (3H, m), 2.08 (3H, m), 1.94 (1H, t, \( J \) 2.6), 1.73 (2H, p, \( J \) 7.4), 1.19 (3H, s); \(^{13}C\) NMR (100 MHz, CDCl\(_3\)): \( \delta \) \( C \) 218.2, 172.6, 137.7, 115.7, 80.3, 78.2, 70.4, 51.9, 34.1, 33.8, 33.1, 25.7, 24.2, 21.3, 20.1; IR \( \nu_{\text{max}} \): 1733 (m, C=O ketone), 1708 (m, C=O ester); HRMS (ESI): [M+H]\(^+\) calcd. for \( C_{15}H_{21}O_3Na \): 249.1485, found: 249.1487.
(1S*,25*)-2-Methyl-3-oxo-2-(prop-2-yn-1-yl)cyclohexyl hex-5-enoate (S11)

According to General Procedure F, syn-8 (111 mg, 0.66 mmol), 5-hexenoic acid (0.11 mL, 0.891 mmol), DMAP (8 mg, 0.066 mmol) and DCC (184 mg, 0.891 mmol) gave a crude material. Purification via flash column chromatography (petroleum ether/EtOAc, 88:12) gave S11 as a colourless oil (164 mg, 0.626 mmol, 95%). Rf = 0.11 (petroleum ether/EtOAc, 92:8); 1H NMR (400 MHz, CDCl3): δH 5.76 (1H, ddt, J17.0, 10.2, 6.7), 5.25 (1H, t, J3.4), 5.07–4.94 (2H, m), 2.12–1.98 (6H, m), 2.12–1.98 (4H, m), 1.96 (t, J2.7), 1.93–1.84 (2H, m), 1.78–1.63 (2H, m), 1.33 (3H, s); 13C NMR (100 MHz, CDCl3): δC 211.9, 172.4, 137.7, 115.7, 80.1, 77.2, 71.4, 50.9, 37.6, 33.8, 33.1, 25.2, 24.2, 23.3, 21.3, 20.9; IR vmax: 1733 (s, C=O), 1710 (s, C=O), 1640 (m, C=C); HRMS (ESI): [M+H]+ calcd. for C16H23O3+: 263.1642, found: 263.1643.

(1S*,25*)-2-Methyl-3-oxo-2-(prop-2-yn-1-yl)cyclopentyl acrylate (31)

According to General Procedure F, syn-1 (136 mg, 0.894 mmol), acrylic acid (82.8 µL, 1.21 mmol), DMAP (16.4 mg, 0.134 µmol) and DCC (249 mg, 1.21 mmol) gave a crude material. Purification via flash column chromatography (EtOAc/petroleum ether, 11:89) gave 31 as a colourless oil (93.7 mg, 0.455 mmol, 51%). Rf = 0.42 (EtOAc/petroleum ether, 20:80); 1H NMR (400 MHz, CDCl3): δH 6.39 (1H, dd, J17.3, 1.4), 6.10 (1H, dd, J17.3, 10.5), 5.86 (1H, dd, J10.5, 1.4), 5.32 (1H, dd, J4.5, 2.1), 2.49–2.38 (4H, m), 2.31 (1H, dddd, J14.8, 10.5, 8.6, 4.5), 2.13 (1H, dddd, J14.8, 7.5, 5.7, 2.1), 1.93 (1H, t, J2.7), 1.20 (3H, s); 13C NMR (101 MHz, CDCl3): δC 218.0, 165.2, 131.5, 128.3, 80.1, 78.6, 70.4, 52.0, 34.1, 25.6, 21.3, 20.2; IR vmax: 3279 (m, C≡C–H), 1743 (s, C=O), 1720 (s, C=O), 1636 (s, C=C); HRMS (ESI): [M+H]+ calcd. for C12H14O3+: 207.1016, found: 207.1013.

(1S*,25*)-2-Methyl-3-oxo-2-(prop-2-yn-1-yl)cyclopentyl 2-azidoacetate (32)

According to General Procedure F, syn-1 (298 mg, 1.96 mmol), 2-azidoacetic (0.198 mL, 2.64 mmol), DMAP (35.9 mg, 0.294 mmol) and DCC (545 mg, 2.64 mmol) gave a crude material. Purification via flash column chromatography (petroleum ether/EtOAc, 83:17) gave 32 as a colourless oil (448 mg, 1.91 mmol, 97%). Rf = 0.26 (petroleum ether/EtOAc, 80:20); 1H NMR (600 MHz, CDCl3): δH 5.38 (1H, dd, J4.6, 2.0), 3.89 (2H, q, Jq 17.2), 2.50–2.42 (2H, m), 2.38 (2H, d, J2.7), 2.38–2.28 (1H, m), 2.13 (1H, dddd, J14.5, 8.1, 4.1, 2.0), 1.96 (1H, t, J2.7), 1.21...
(1S*,2S*)-2-methyl-3-oxo-2-(prop-2-yn-1-yl)cyclopentyl 4-azidobutanoate (33)

According to General Procedure F, syn-1 (100 mg, 0.66 mmol), 4-azidobutanoic acid (115 mg, 0.891 mmol), DMAP (8 mg, 0.066 mmol) and DCC (184 mg, 0.891 mmol) gave a crude material. Purification via flash column chromatography (hexane/EtOAc, 12:88) gave 33 as a colourless oil (145 mg, 0.55 mmol, 84%). \( R_f = 0.11 \) (hexane/EtOAc, 92:8); \( ^1H\) NMR (400 MHz, CDCl\(_3\)): \( \delta_H 5.27 \) (1H, dd, \( J \) 4.6, 1.9), 3.36 (2H, t, \( J \) 6.7), 2.42 (4H, m), 2.38 (2H, d, \( J \) 2.7), 2.29 (1H, m), 2.12–2.03 (1H, m), 1.96–1.87 (3H, m), 1.19 (3H, s); \( ^{13}C\) NMR (100 MHz, CDCl\(_3\)): \( \delta_C 217.9, 171.8, 80.3, 78.6, 71.4, 50.9, 50.7, 37.6, 31.4, 25.2, 24.4, 23.3, 21.4, 20.9; \) IR \( \nu_{max} \): 2099 (s, N=N=N), 1733 (s, C=O), 1709 (s, C=O); HRMS (ESI): [M+H]\(^+\) calcd for C\(_{13}\)H\(_{20}\)O\(_3\)N\(_3\)\(^+\): 278.1499, found: 278.1488.

(1S*,2S*)-2-Methyl-3-oxo-2-(prop-2-yn-1-yl)cyclohexyl 4-azidobutanoate (S12)

According to General Procedure F, syn-8 (111 mg, 0.66 mmol), 4-azidobutanoic acid (115 mg, 0.891 mmol), DMAP (8 mg, 0.066 mmol) and DCC (184 mg, 0.891 mmol) gave a crude material. Purification via flash column chromatography (hexane/EtOAc, 88:12) gave S12 as a colourless oil (155 mg, 0.56 mmol, 85%). \( R_f = 0.11 \) (hexane/EtOAc, 92:8); \( ^1H\) NMR (400 MHz, CDCl\(_3\)): \( \delta_H 5.27 \) (1H, dd, \( J \) 4.1, 2.7), 3.34 (2H, td, \( J \) 6.7, 1.4), 2.67–2.30 (6H, m), 1.97 (1H, t, \( J \) 2.7), 1.93–1.85 (4H, m), 1.33 (3H, s); \( ^{13}C\) NMR (100 MHz, CDCl\(_3\)): \( \delta_C 211.7, 171.5, 80.1, 77.6, 71.4, 50.9, 50.7, 37.6, 31.4, 25.2, 24.4, 23.3, 21.4, 20.9; \) IR \( \nu_{max} \): 2097 (s, N=N=N), 1733 (s, C=O), 1709 (s, C=O); HRMS (ESI): [M+H]\(^+\) calcd for C\(_{14}\)H\(_{20}\)O\(_3\)N\(_3\)\(^+\): 292.1651, found: 292.1649.

(9aS*,12aS*,Z*)-9a-methyl-8-methylene-4,5,8,9,9a,11,12,12a-octahydro-2H-cyclopenta[b][1]oxacycloundecene-2,10(3H)-dione (34)

Grubbs 2\(^{nd}\) generation catalyst (30 mg, 35.3 µmol) was added to a stirred solution of 30 (138 mg, 0.56 mmol) in PhMe (70 mL). The reaction mixture was stirred under an ethylene atmosphere at reflux for 4 h, then degassed
with N₂ and stirred for a further 16 h. The resultant mixture was filtered through celite then concentrated in vacuo. Purification via flash column chromatography (petroleum ether/EtOAc, 90:10) gave 34 as a white amorphous solid (117 mg, 0.47 mmol, 85%). Rf = 0.24 (Petroleum ether/EtOAc, 90:10); ¹H NMR (400 MHz, CDCl₃): δH 5.91 (1H, d, J 15.8), 5.63 (1H, dt, J 15.6, 7.7), 5.17–4.99 (2H, m), 4.84 (1H, d, J 2.0), 2.50–2.09 (8H, m), 2.08–1.80 (4H, m), 1.10 (3H, s); ¹³C NMR (101 MHz, CDCl₃): δC 220.2, 175.1, 142.4, 136.5, 128.1, 116.3, 77.4, 53.4, 35.4, 34.4, 33.8, 31.4, 26.2, 24.8, 22.0; IR νmax: 1729 (m, C=O); HRMS (ESI): [M+H]⁺ calcd. for C₁₅H₂₁O₃: 249.1485, found: 249.1491.

(9aS*,13aS*,Z*)-9a-Methyl-8-methylene-3,4,5,8,9a,11,12,13,13a-decahydrobenzo[b][1]oxacycloundecine-2,10-dione (S13)

Grubbs 2nd generation catalyst (9.5 mg, 11 µmol) was added to a stirred solution of S11 (45 mg, 0.17 mmol) in PhMe (22 mL). The reaction mixture was stirred under an ethylene atmosphere at reflux for 4 h, then degassed with N₂ and stirred for a further 16 h. The resultant mixture was filtered through celite then concentrated in vacuo. Purification via flash column chromatography (petroleum ether/EtOAc, 90:10) gave S13 as a white amorphous solid (37 mg, 0.14 mmol, 83%). Rf = 0.26 (petroleum ether/EtOAc, 90:10); ¹H NMR (400 MHz, CDCl₃): δH 5.93 (1H, d, J 15.9), 5.12 (1H, s), 4.84 (1H, t, J 1.5), 4.77–4.70 (1H, m), 2.64 (1H, ddd, J 15.1, 12.7, 7.3), 2.38–2.14 (6H, m), 2.05–1.81 (7H, m), 1.31 (3H, s); ¹³C NMR (101 MHz, CDCl₃): δC 213.9, 175.3, 142.2, 135.7, 116.2, 51.9, 37.7 (2C), 33.2, 29.8, 25.2, 24.7, 23.8, 20.8; IR νmax: 1726 (s, C=O), 1706 (s, C=O); HRMS (ESI): [M+H]⁺ calcd. for C₁₆H₂₂O₃: 263.1642, found: 263.1643.

(3R*,8aS*,11aS*)-8a-Methyl-3,4,5,8,8a,10,11,11a-octahydro-3,7-methanocyclopenta[b]oxecine-2,9-dione (35)

Hoveyda-Grubbs 2nd generation catalyst (11.6 mg, 18.4 µmol) was added to a stirred solution of S11 (38.0 mg, 0.184 mmol) in PhMe (37 mL). The reaction mixture was stirred under an ethylene atmosphere at reflux for 4 h, then concentrated in vacuo. Purification via flash column chromatography (petroleum ether/EtOAc, 89:11) gave 35 as a colourless oil (37.5 mg, 0.160 mmol, 87%). Rf = 0.42 (petroleum ether/EtOAc, 80:20); ¹H NMR (400 MHz, CDCl₃): δH 5.70 (1H, ddd, J 8.0, 3.8, 1.6), 5.08 (1H, t, J 2.9), 3.11 (1H, dt, J 14.2, 1.6), 2.99–2.90 (1H, m), 2.44–2.36 (2H, m), 2.35–2.15 (4H, m), 2.15–2.05 (1H, m), 1.88 (1H, d, J 14.2), 1.81–1.68 (2H, m), 1.55–1.45 (1H, m), 0.94 (3H, s); ¹³C NMR (101 MHz, CDCl₃): δC 219.2, 178.9, 137.8, 126.5, 85.2, 57.9, 44.0, 39.7, 38.7, 34.7, 26.0, 23.6, 23.2, 22.5; IR νmax: 1729 (s, C=O); HRMS (ESI): [M+H]⁺ calcd. for C₁₄H₁₉O₃: 235.1329, found: 235.1334.
Cp*RuCl(COD) (13.9 mg, 36.6 µmol) was added to a degassed solution of 32 (43.0 mg, 0.183 mmol) in PhMe (180 mL). The resultant solution heated under refluxed for 16 h before being cooled to rt. The crude mixture was filtered through celite and concentrated in vacuo. Purification via flash column chromatography (CH₂Cl₂/MeOH, 96:4) gave 36 as a colourless oil (38.0 mg, 0.162 mmol, 88%). R_f = 0.38 (CH₂Cl₂/MeOH, 95:5); ^1H NMR (400 MHz, CD₃OD): δ_H 7.61 (1H, s), 5.44 (1H, d, J = 17.8), 5.34 (1H, d, J = 17.8), 3.92 (1H, dd, J = 4.2, 2.3), 2.88 (1H, d, J = 15.4), 2.80 (1H, d, J = 15.4), 2.41–2.13 (2H, m), 2.25–2.13 (1H, m), 1.86 (1H, dddd, J = 14.1, 7.6, 4.6, 2.3), 0.94 (3H, s); ^13C NMR (101 MHz, CD₃OD): δ_C 221.9, 169.1, 137.2, 134.6, 76.7, 54.7, 49.8, 34.1, 28.8, 24.9, 19.9; IR v_max: 1736 (m, C=O); HRMS (ESI): [M-H]^- calcd. for C₁₁H₁₂N₃O₃-: 234.0884, found 234.0879.

Cp*RuCl(COD) (17 mg, 45 µmol) was added to a degassed solution of 33 (82 mg, 0.31 mmol) in PhMe (120 mL). The resultant solution heated under refluxed for 16 h before being cooled to rt. The crude mixture was filtered through celite and concentrated in vacuo. Purification via flash column chromatography (CH₂Cl₂/MeOH, 97:3) gave 37 as an amorphous yellow solid (71 mg, 0.27 mmol, 87%). R_f = 0.24 (Hexane/EtOAc, 90:10); ^1H NMR (400 MHz, CDCl₃): δ_H 7.47 (1H, s), 4.27 (2H, app s), 3.01 (1H, app s), 2.85–2.29 (7H, m), 2.30–2.14 (2H, m), 2.02–1.91 (1H, m), 1.26 (3H, s); ^13C NMR (101 MHz, CDCl₃): δ_C 218.4, 170.8, 134.3, 132.8, 78.4, 52.9, 45.7, 34.4, 29.7, 29.3, 26.5, 25.8, 22.0; IR v_max: 1736 (m, C=O); HRMS (ESI): [M+H]^+ calcd. for C₁₃H₁₈N₃O₃+: 264.1343, found 264.1345.
(9S*,13aS*)-13a-Methyl-6,7,9a,10,11,12,13a,14-octahydro-13H-benzo[b][1,2,3]triazolo[5,1-e][1,6]oxazecine-8,13(5H)-dione (S14)

[RuCp*Cl]₄ (42 mg, 38.6 μmol) was added to a degassed solution of S12 (92 mg, 0.33 mmol) in PhMe (134 mL). The resultant solution heated under reflux for 24 h before being cooled to rt. The crude mixture was filtered through celite and concentrated in vacuo. Purification via flash column chromatography gave S14 as an amorphous yellow solid (78 mg, 0.28 mmol, 85%). Rf = 0.20 (Hexane/EtOAc, 90:10); ¹H NMR (400 MHz, CDCl₃): δH 7.52 (1H, s), 4.42 (2H, m), 4.29–4.17 (1H, m), 3.36 (1H, d, J = 15.6), 2.86–2.55 (3H, m), 2.47–2.29 (4H, m), 2.02–1.79 (4H, m), 1.46 (3H, s); ¹³C NMR (101 MHz, CDCl₃): δC 212.8, 171.0, 133.4, 132.4, 77.4, 50.9, 46.8, 37.6, 33.8, 27.5, 26.9, 25.4, 23.2, 20.9; IR νmax: 1735 (s, C=O), 1703 (s, C=O); HRMS (ESI): [M+H]⁺ calcd. for C₁₄H₂₀N₃O₃⁺: 278.1499, found 278.1499.

(5S*,6S*)-5-Hydroxy-6-methyl-6-(prop-2-yn-1-yl)tetrahydro-2H-pyran-2-one (38)

KHCO₃ (82.7 mg, 0.826 mmol) and mCPBA (<77%, 1.02 g, 4.13 mmol) were added to a solution of syn-1 (110 mg, 0.413 mmol) in anhydrous CH₂Cl₂ and the reaction mixture was stirred at reflux for 40 h. The mixture was concentrated in vacuo and filtered through a short plug of silica. TBAF (1.0 M in THF, 0.657 mL, 0.657 mmol) was added to a solution of the crude Baeyer–Villiger oxidation product in anhydrous THF (5 mL). The mixture was stirred at rt for 2 h, then concentrated in vacuo. Purification via flash column chromatography (petroleum ether/EtOAc/AcOH, 49:49:2) gave 38 as a colourless oil (20.2 mg, 0.120 mmol, 29%); Rf = 0.36 (petroleum ether/EtOAc, 50:50); ¹H NMR (400 MHz, CDCl₃): δH 4.56 (1H, dd, J = 7.9, 7.2), 2.64–2.50 (4H, m), 2.29 (2H, dddd, J = 12.9, 9.9, 9.2, 7.9), 2.18 (1H, dddd, J = 12.9, 9.9, 7.9, 4.5), 2.08 (1H, t, J = 2.7), 1.27 (3H, s); ¹³C NMR (101 MHz, CDCl₃): δC 177.2, 83.6, 79.8, 72.4, 71.6, 30.2, 29.0, 22.1, 21.7; IR νmax: 3452 (br., O–H), 3285 (s, C≡C–H), 1754 (s, C=O); HRMS (ESI): [M+H]⁺ calcd. for C₉H₁₃O₃⁺: 169.0859, found 169.0859.
(4aS*,7aS*)-4a-Methyl-4a,6,7,7a-tetrahydrocyclopenta[b]pyran-5(4H)-one (39)

CpRu(PPh₃)₂Cl (57 mg, 0.079 mmol) and PPh₃ (42 mg, 0.16 mmol) were added to a degassed solution of N-hydroxy succinimide (45 mg, 0.40 mmol), NBu₄PF₆ (40 mg, 0.1 mmol), NaHCO₃ (34 mg, 0.40 mmol) and syn-1 (120 mg, 0.79 mmol) in DMF (8 mL). The reaction was degassed once more and then sealed in a vial. The resultant mixture was stirred at 80 °C for 18 hours. Further CpRu(PPh₃)₂Cl (57 mg, 0.079 mmol) was added and the reaction was stirred at 80 °C for 38 hours. Upon completion, the reaction was filtered through celite and partitioned between EtOAc (20 mL) and brine (20 mL). The organic layer was separated, dried and concentrated in vacuo. Purification via flash column chromatography (hexane/EtOAc, 90:10) gave 39 as a colourless oil (78 mg, 0.51 mmol, 65%). Rₛ = 0.30 (hexane/EtOAc, 90:10); ¹H NMR (400 MHz, CDCl₃): δH 6.32 (1H, dt, J₆.₃, 2.₁), 4.62 (1H, ddd, J₆.₃, 4.₃, 3.₂), 4.17 (1H, t, J 3.₇), 2.48–2.₃₀ (3H, m), 2.₂₈–2.₁₉ (1H, m), 2.₁₃–2.₀₆ (1H, m), 1.₈₂–1.₇₇ (1H, m), 1.₀₇ (3H, s); ¹³C NMR (101 MHz, CDCl₃): δC 21₈.₀, 1₄₂.₆, ₉₈.₄, ₇₉.₇, ₄₇.₅, ₃₃.₀, ₂₅.₈, ₂₄.₆, ₂₁.₈; IR vₘₐₓ: 1₇₄₂ (s, C=O), 1₆₅₉ (m, C=C); HRMS (ESI): [M+H]+ calcd. for C₉H₁₃O₂+: 1₅₃.₀₉₁₀, found: 1₅₃.₀₉₁₀.

(4aS*,8aS*)-4a-Methyl-4a,4a,6,7,8a-hexahydro-5H-chromen-5-one (S15)

CpRu(PPh₃)₂Cl (61 mg, 0.084 mmol) and PPh₃ (45 mg, 0.17 mmol) were added to a degassed solution of N-hydroxy succinimide (48 mg, 0.43 mmol), NBu₄PF₆ (43 mg, 0.11 mmol), NaHCO₃ (36 mg, 0.43 mmol) and syn-8 (140 mg, 0.84 mmol) in DMF (8.5 mL). The reaction was degassed once more and then sealed in a vial. The resultant mixture was stirred at 80 °C for 18 hours. Further CpRu(PPh₃)₂Cl (61 mg, 0.084 mmol) was added and the reaction was stirred at 80 °C for 38 hours. Upon completion, the reaction was filtered through celite and partitioned between EtOAc (20 mL) and brine (20 mL). The organic layer was separated, dried and concentrated in vacuo. Purification via flash column chromatography (hexane/EtOAc, 90:10) gave S15 as a colourless oil (88 mg, 0.53 mmol, 63%). Rₛ = 0.30 (elucent hexane/EtOAc, 90:10); ¹H NMR (400 MHz, CDCl₃): δH 6.2₆ (1H, dt, J 6.₂, 2.₀), 4.₆₃ (1H, ddd, J 6.₂, 4.₅, 3.₀), 3.₉₆ (1H, dd, J ₅.₅, 2.₂), 2.₆₁–2.₄₄ (2H, m), 2.₄₁–2.₃₀ (1H, m), 2.₁₅–2.₀₀ (2H, m), 1.₉₉–1.₈₇ (1H, m), 1.₈₅–1.₇₂ (1H, m), 1.₆₀ (1H, dt, J 1₇.₂, 2.₆), 1.₂₀ (3H, s); ¹³C NMR (101 MHz, CDCl₃): δC 2₁₂.₂₀, 1₄₂.₄, ₉₈.₈, ₈₀.₀, ₄₇.₆, ₃₆.₉, ₂₇.₇, ₂₅.₈, ₂₃.₀, ₂₀.₀; IR vₘₐₓ: 1₇₀₈ (s, C=O), 1₆₆₁ (m, C= C); HRMS (ESI): [M+H]+ calcd. for C₁₀H₁₅O₂+: 1₆₇.₁₀₆₇, found: 1₆₇.₁₀₆₆.
(4aS*,7aS*)-4a-{Cyclopropylmethyl}-4a,6,7,7a-tetrahydrocyclopenta[b]pyran-5(4H)-one (S16)

CpRu(PPh₃)₂Cl (32.3 mg, 40.6 µmol) and PPh₃ (10.6 mg, 40.6 µmol) were added to a degassed solution of N-hydroxy succinimide (11.7 mg, 0.101 mmol), NBu₄PF₆ (10.2 mg, 26.4 µmol), NaHCO₃ (8.5 mg, 0.101 mmol) and syn-9 (39.0 mg, 0.203 mmol) in DMF (4 mL). The reaction was degassed once more and then sealed in a vial. The resultant mixture was stirred at 80 °C for 18 hours. The reaction was filtered through celite and partitioned between EtOAc (20 mL) and brine (20 mL). The organic layer was separated, dried and concentrated in vacuo.

Purification via flash column chromatography (petroleum ether/EtOAc, 90:10) gave S16 as a colourless oil (19.1 mg, 0.099 mmol, 49%). R_f = 0.46 (petroleum ether/EtOAc, 90:10); ¹H NMR (400 MHz, CDCl₃) δH 6.31 (1H, dt, J 6.3, 2.1), 4.64 (1H, dt, J 6.3, 3.7), 4.48 (1H, t, J 4.0), 2.45 (1H, ddd, J 18.1, 9.2, 6.7), 2.37–2.18 (3H, m), 2.11–2.01 (1H, m), 1.95 (1H, dddd, J 17.7, 4.0, 2.1, 0.7), 1.40 (2H, d, J 6.7), 0.67 (1H, dddt, J 14.3, 8.4, 6.9, 4.9), 0.52–0.40 (2H, m), 0.10– –0.04 (2H, m); ¹³C NMR (101 MHz, CDCl₃) δC 217.3, 142.3, 98.2, 77.6, 51.5, 39.1, 33.5, 25.7, 22.8, 6.1, 4.9, 4.8; IR νmax: 3066 (m, C=C–H), 1740 (s, C=O), 1660 (s, C=C), 1236 (s, C=C–O–C), 1063 (s, C=C–O–C); HRMS (ESI): [M+H]+ calcd. for C₁₂H₁₇O₂ [M + H]^+: 193.1223, found 193.1232.

(2S*,3aS*,6aS*)-2-Methoxy-2,3a-dimethylhexahydro-4H-cyclopenta[b]furan-4-one (40a) and (2R*,3aS*,6aS*)-2-methoxy-2,3a-dimethylhexahydro-4H-cyclopenta[b]furan-4-one (40b)

[Ir(cod)Cl]₂ (4 mg, 0.005 mmol) was added to a stirred solution of syn-1 (33 mg, 0.22 mmol) in MeOH (0.6 mL). The resultant mixture was stirred at rt for 4 hours. Upon completion, the reaction was filtered through celite and concentrated in vacuo to give a mixture of diastereomers (22:78 dr). Purification via flash column chromatography (hexane/EtOAc, 90:10) gave 40a (7 mg, 18%) and 40b (23 mg, 58%) both as colourless oils.

Data of 40a:
R_f = 0.24 (hexane/EtOAc, 90:10); ¹H NMR (400 MHz, CDCl₃): 4.35 (1H, app d, J 4.3), 3.21 (3H, s), 2.54–2.42 (1H, m), 2.37–2.27 (1H, m), 2.25–2.13 (2H, m), 2.04–1.94 (2H, m), 1.33 (3H, s), 1.15 (3H, s); ¹³C NMR (126 MHz, CDCl₃): δC 222.9, 108.3, 86.6, 56.5, 50.8, 48.7, 34.6, 24.0, 21.5, 18.6; IR νmax: 1738 (s, C=O); HRMS (ESI): [M+Na]^+: calcd. for C₁₀H₁₆O₃Na+: 207.0992, found: 207.0993.

Data of 40b:
R_f = 0.13 (hexane/EtOAc, 90:10); ¹H NMR (400 MHz, CDCl₃): δH 4.47 (1H, app d, J 5.1), 3.13 (3H, s), 2.59–2.41 (2H, m), 2.37–2.23 (1H, m), 2.20–2.01 (2H, m), 1.79 (1H, d, J 12.7), 1.39 (3H, s), 1.12 (3H, s); ¹³C NMR (126 MHz, CDCl₃): δC 221.9, 107.7, 88.8, 55.5, 50.8, 48.4, 35.3, 26.2, 20.9, 19.4; IR νmax: 1739 (s, C=O); HRMS (ESI): [M+H]^+: calcd. for C₁₀H₁₆O₃Na+: 207.0992, found: 207.0998.
Methyl (E)-2-[(3aS*, 6aS*)-3a-Methyl-4-oxohexahydro-2H-cyclopenta[b]furan-2-ylidene]acetate (41)

A CO atmosphere was introduced to a stirred solution of Pd(CH$_3$CN)$_2$Cl$_2$ (30.2 mg, 0.117 mmol) and p-benzoquinone (277 mg, 2.57 mmol) in anhydrous MeOH (30 mL). The mixture was cooled to 50 °C and then added dropwise a solution of syn-1 (355 mg, 2.33 mmol) in anhydrous MeOH (15 mL). The reaction mixture was stirred under a CO atmosphere at –50 °C for 16 h. The mixture was allowed to warm to 22 °C then diluted with CH$_2$Cl$_2$ (200 mL). The mixture was washed with 1 M NaOH (1 × 200 mL), dried and concentrated in vacuo. Purification via flash column chromatography (petroleum ether/EtOAc, 80:20) gave 41 as a colourless oil (160 mg, 0.762 mmol, 33%). $R_f = 0.40$ (petroleum ether/EtOAc, 70:30); $^1$H NMR (600 MHz, CDCl$_3$) $\delta$H 5.26 (1H, dd, $J$ 2.3, 1.5), 4.72 (1H, dd, $J$ 4.2, 1.0), 3.67–3.62 (4H, m), 2.86 (1H, dd, $J$ 18.9, 2.3), 2.43–2.34 (3H, m), 2.18–2.10 (1H, m), 1.22 (3H, s); $^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$C 219.4, 174.0, 168.4, 91.0, 90.6, 54.2, 51.0, 42.0, 34.5, 25.0, 18.0; IR $\nu_{max}$: 1741 (s, C=O), 1701 (s, C=O), 1637 (s, C=C); HRMS (ESI): [M + H]$^+$ calcd. for C$_{11}$H$_{15}$O$_4$: 211.0965, found 211.0972.
3. COMPUTATIONAL ANALYSIS

A) Compound Collections Analysed

Collection 1: This Work.
Only final compounds in their fully deprotected forms were analysed. The relevant structures are shown in Fig. 1.
Collection 2: Maybridge ‘Ro3’ Diversity Set 1 Fragment Collection
This library is based on the Maybridge ‘Ro3’ Diversity Set 1 within the Maybridge Fragment collection. Details of the library (including SMILES and SDF) are available from ‘http://www.maybridge.com/’ under the Fragment collection ‘Maybridge Ro3 Diversity Sets’ section.

Collection 3: Life Chemicals 3D Fragment Library
This library is based on the 3D Fragment library within the Life chemicals Fragment collection. Details of the library (including SMILES and SDF) are available from ‘http://www.lifechemicals.com/’ under the Fragment libraries ‘3D fragment library’ section.

B) Calculation of Physicochemical Properties
Calculation of the physicochemical properties of library members was carried out using a Molecular Operating Environment (MOE) software package version 2012.10 from the Chemical Computing Group. Merck molecular force field Amber 10 EHT, an all-atom force field parameterised for small organic molecules with the Generalised Born solvation model, was used to minimise the energy potential. A LowModeMD search was employed for conformation generation. Detailed settings for conformational search are listed below.

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<tr>
<th>Conformation Search Settings</th>
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Our library compounds were analysed for the following properties: SlogP, molecular weight (MW), number of hydrogen-bond acceptors (HBA), number of hydrogen-bond donors (HBD), number of chiral centres and fraction aromatic (the number of aromatic atoms expressed as a fraction of the total number of heavy atoms). Fraction $sp^3$ (the number of $sp^3$ hybridised carbon atoms expressed as a fraction of the total number of carbon atoms) was calculated using the LLAMA web tool. The distribution of these data and the mean values are displayed in a series of histograms in Fig 2.

By means of comparison with existing libraries, the percentage of the library complying with the fragment ‘rule of three’ properties is shown alongside those of two popular commercially available fragment libraries, Maybridge Diversity Set 1 and Life Chemicals 3D, in Table 1.

**Fig. 2:** Histograms showing the distribution of physicochemical properties amongst the compounds in Fig. 1.
Table 1. Percentage of each library complying with the fragment ‘rule of three’.

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<th>Life Chemicals 3D</th>
<th>Ideal Value[a]</th>
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<td>SlogP</td>
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<tr>
<td>HBD</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>≤3</td>
</tr>
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</table>

[a] MW = molecular weight, HBA = number of hydrogen bond acceptors, HBD = number of hydrogen bond donors. [b] Ideal range based on guidelines of ‘rule of three’.

C) Principal Moment of Inertia

The principal moments of inertia (PMI) of the lowest energy conformations of the virtual library was performed using the LLAMA web tool and the data replotted in excel.

Table 2. Normalised PMI ratio values of conformers of fig. 1 compounds with the lowest energy.

<table>
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<th>Compound</th>
<th>Canonical SMILES</th>
<th>PMI x (npr1)</th>
<th>PMI y (npr2)</th>
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<td>O[C@H][([C@@]1[CC#C])CCC1=O]</td>
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<tr>
<td>anti-1</td>
<td>O[C@@H][([C@H]1[CC#C])CCC1=O]</td>
<td>0.44513</td>
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<td>syn-8</td>
<td>O[C@H][([C@@]1[CC#C])CCC1=O]</td>
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<tr>
<td>anti-8</td>
<td>O[C@H][([C@H]1[CC#C])CCC1=O]</td>
<td>0.42554</td>
<td>0.75246</td>
</tr>
<tr>
<td>syn-9</td>
<td>O[C@H][([C@@]1[CC#C])CCC1=O]</td>
<td>0.58255</td>
<td>0.78519</td>
</tr>
<tr>
<td>anti-9</td>
<td>O[C@H][([C@@]1[CC#C])CCC1=O]</td>
<td>0.54026</td>
<td>0.78265</td>
</tr>
<tr>
<td>10</td>
<td>O[C@H][([C@@]1[CC#C])CCC1=O]</td>
<td>0.50541</td>
<td>0.88669</td>
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<tr>
<td>12</td>
<td>O[C@H][([C@@]1[CC#C])CCC1=O]</td>
<td>0.50782</td>
<td>0.70959</td>
</tr>
<tr>
<td>13a</td>
<td>O[C@H][([C@@]1[CC#C])CCC1=O]</td>
<td>0.31222</td>
<td>0.94676</td>
</tr>
<tr>
<td>13b</td>
<td>O[C@H][([C@@]1[CC#C])CCC1=O]</td>
<td>0.30808</td>
<td>0.94576</td>
</tr>
<tr>
<td>S17a</td>
<td>O[C@H][([C@@]1[CC#C])CCC1=O]</td>
<td>0.39961</td>
<td>0.88123</td>
</tr>
<tr>
<td>S17b</td>
<td>O[C@H][([C@@]1[CC#C])CCC1=O]</td>
<td>0.31094</td>
<td>0.84209</td>
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<tr>
<td>17</td>
<td>O[C@H][([C@@]1[CC#C])CCC1=O]</td>
<td>0.32122</td>
<td>0.94676</td>
</tr>
<tr>
<td>18b</td>
<td>O[C@H][([C@@]1[CC#C])CCC1=O]</td>
<td>0.381</td>
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<tr>
<td>18a</td>
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<td>0.93321</td>
</tr>
<tr>
<td>20</td>
<td>O[C@H][([C@@]1[CC#C])CCC1=O]</td>
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<tr>
<td>21</td>
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<td>0.79301</td>
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<tr>
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<td>O[C@H][([C@@]1[CC#C])CCC1=O]</td>
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<td>0.73635</td>
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<tr>
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<td>O[C@H][([C@@]1[CC#C])CCC1=O]</td>
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<td>0.75436</td>
</tr>
<tr>
<td>25</td>
<td>O[C@H][([C@@]1[CC#C])CCC1=O]</td>
<td>0.18636</td>
<td>0.90693</td>
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<tr>
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<td>O[C@H][([C@@]1[CC#C])CCC1=O]</td>
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<tr>
<td>anti-26</td>
<td>O[C@H][([C@@]1[CC#C])CCC1=O]</td>
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<tr>
<td>27</td>
<td>O[C@H][([C@@]1[CC#C])CCC1=O]</td>
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<td>29</td>
<td>O[C@H][([C@@]1[CC#C])CCC1=O]</td>
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</tr>
<tr>
<td>34</td>
<td>O[C@H][([C@@]1[CC#C])CCC1=O]</td>
<td>0.4175</td>
<td>0.74513</td>
</tr>
</tbody>
</table>
D) Natural Product-Likeness

The natural product-likeness of molecules was calculated using the open-source and open-data “Natural-Product-Likeness Scorer” based on a previously developed algorithm.6,7 This Bayesian measure evaluates how similar a molecule is to the structural space covered by natural products. The algorithm removes small disconnected fragments (e.g. counter ions and metals) and divides each compound into smaller substructures, which are compared to two training sets consisting of: 1) 113,425 synthetic lead-like compounds selected from the ZINC database8 and 2) 58,018 natural products derived from the Traditional Chinese Medicinal Database @ Taiwan9 and the ChEMBL database (only Journal of Natural Products structures selected).10 On a logarithmic scale, each molecule is assigned a score (typically in the range of −3 to 3) based on the resemblance of its substructures to the two training sets. Positive values indicate higher resemblance to natural products and negative values indicate a more synthetic character. For full experimental details see references.5,6 The NuBBE database of 2712 natural products was used as the source for natural products.11
4. REFERENCES

5. NMR SPECTRA