Synthesis of Structurally Diverse N-Substituted Quaternary-Carbon-Containing Small Molecules from α,α-Disubstituted Propargyl Amino Esters

Natalia Mateu*, [a] Sarah L. Kidd*, [a] Leen Kalash, [a] Hannah F. Sore, [a] Andrew Madin, [b] Andreas Bender, [a] and David R. Spring* [a]

chem_201803143_sm_misellaneous_information.pdf
Synthesis of structurally diverse N-substituted quaternary carbon containing small molecules from α,α-disubstituted propargyl amino esters

Natalia Mateu‡, Sarah L. Kidd‡, Leen Kalash, Hannah Sore, Andrew Madin, Andreas Bender and David R. Spring*

Department of Chemistry, University of Cambridge
Lensfield Road, Cambridge, CB2 1EW, UK

*E-mail: spring@ch.cam.ac.uk
*E-mail: nm462@cam.ac.uk

SUPPORTING INFORMATION

TABLE OF CONTENTS

SUPPLIMENTARY FIGURES ........................................................................................................2
GENERAL REMARKS .................................................................................................................6
PROCEDURES AND ANALYTICAL DATA ..................................................................................8
STEREOCHEMICAL AND STRUCTURAL ASSIGNMENTS .........................................................60
  Compounds 2 and 3 ..................................................................................................................60
  Compound 14 .........................................................................................................................61
  Compound 16 .........................................................................................................................61
COMPUTATIONAL ANALYSIS ............................................................................................63
  A) Principal Moment of Inertia (PMI) ..................................................................................63
      General details ....................................................................................................................63
  B) Computational evaluation of physicochemical properties ................................................76
      General details ....................................................................................................................76
  C) Multi-Dimensional Scaling (MDS) Plot Generation .........................................................78
      Selection of ChEMBL 20 compounds .............................................................................78
      Multi-Dimensional Scaling (MDS) analysis .....................................................................78
NMR SPECTRA ..........................................................................................................................79
Scheme S1.
Diversity-oriented synthesis strategy used to access compounds 2 – 33
Scheme S1. Diversity-oriented synthesis strategy used to access compounds 2 – 33 (cont.)
Figure S1. The 27 molecular frameworks featured within DOS library.
GENERAL REMARKS

All non-aqueous reactions were performed in dry glassware under a stream of Argon using anhydrous solvents. Tetrahydrofuran was dried over sodium wire and distilled from a mixture of lithium aluminium hydride and calcium hydride with triphenylmethane as the indicator. Dichloromethane, toluene and methanol were all distilled from calcium hydride. Petroleum ether was distilled before use and refers to the fraction between 40-60 °C; anhydrous DMF and DCE were purchased from Aldrich and used as received. All reagents were obtained from commercial suppliers and used without further purification. Reactions were carried out at ambient temperature unless otherwise stated. All temperatures below 0 °C are achieved with an external bath: those of 0 °C were maintained using an ice/water bath, those of lower temperatures using a dry ice/ DMF bath.

Yields refer to chromatographically and spectroscopically pure compounds unless otherwise stated. Analytical thin layer chromatography (TLC) was performed on commercially available glass pre-coated Merck Kiesel gel 60 F254 plates. Visualisation was by quenching of UV fluorescence (λ, max = 254 nm) or by staining with potassium permanganate. Rf values are quoted to the nearest 0.01. Where possible, reactions were monitored using TLC. Flash column chromatography was performed using slurry-packed SiO₂ (Merck Grade 9385, 230-400 mesh) under a positive pressure of N₂. Melting points were obtained on a Buchi B-545 melting point apparatus and are uncorrected. Optical rotations were measured on an Anton Paar MCP 100 Modular Compact Polarimeter. Proton nuclear magnetic resonance spectra (¹H NMR) were recorded using an internal deuterium lock at ambient probe temperatures (unless otherwise stated) on the following instruments: Bruker DPX-400 (400 MHz), Bruker Avance 400 QNP (400 MHz), Bruker BB 500 (500 MHz) and Bruker Avance 500 Cryo Ultrashield (500 MHz). Chemical shifts (δH) are referenced to the residual non-deuterated solvent peak and quoted in parts per million (ppm) to the nearest 0.01 ppm. Coupling constants are quoted in Hertz to the nearest 0.1 Hz. Data are reported in the format: chemical shift, integration, multiplicity [app = apparent; br = broad; s = singlet; d = doublet; t
= triplet; q = quartet; quin = quintet; m = multiplet; or as a combination of these, e.g. dd],
coupling constant(s), assignment. Proton assignments are determined either on the basis of
unambiguous chemical shift, coupling patterns, by patterns observed in the two-dimensional
experiments (1H-1H COSY, HMBC and HMQC) or by analogy to fully interpreted spectra for
related compounds. Carbon nuclear magnetic resonance spectra ($^{13}$C NMR) were recorded
by broadband proton spin decoupling at ambient probe temperatures (unless otherwise
stated) using an internal deuterium lock on the following instruments: Bruker DPX-400 (100
MHz), Bruker Avance 400 QNP (100 MHz), Bruker BB 500 (125 MHz) and Bruker Avance
500 Cryo Ultrashield (125 MHz). Chemical shifts ($\delta$C) are referenced to the residual non-
deuterated solvent peak and quoted in parts per million (ppm) to the nearest 0.1 ppm.
Assignments are supported by either chemical shift, APT/DEPT, two dimensional
experiments (HMBC and HMQC) or by analogy to fully interpreted spectra for related
compounds. High resolution mass spectrometry (HRMS), measurements were carried out
on a Micromass LCT Premier spectrometer using electron spray ionisation (ESI) techniques.
Masses are quoted within the error limits of ±5ppm mass units.
PROCEDURES AND ANALYTICAL DATA

Synthesis of methyl 2-amino-2-methylpent-4-ynoate (1)

Following a modified version of a reported procedure,¹ methyl pyruvate (4.85 mL, 53.6 mmol) and p-anisidine (4.40 g, 35.7 mmol) were dissolved in MeCN (35 mL) and the mixture was heated at 50 °C for 1 hour. Then, the solvent was removed under reduced pressure and the crude product was dissolved in a mixture of petroleum ether/CH₂Cl₂ (10:1). The grey precipitate formed was removed by filtration and the filtrate was concentrated in vacuo. The resulting green oil was dissolved in DMF (158 mL) and the mixture was cooled to 0 °C. Propargyl bromide (80% wt. % in toluene, 4.77 mL, 42.9 mmol) and activated zinc powder (3.5 g, 53.6 mmol) were added. The reaction mixture was then warmed to room temperature and then heated to 60 °C. After 1 hour the medium was cooled to 0 °C, hydrolysed with a saturated aqueous solution of NH₄Cl and extracted with EtOAc (3x). The combined organic layers were washed with brine, dried with Na₂SO₄, filtered, and the solvent evaporated. The residue was purified by flash column chromatography (silica gel; petroleum ether/EtOAc, 5:1) to afford 5.65 g of S1 (64% yield) as a yellow oil. The spectroscopic data are in agreement with those previously reported in the literature.¹ HRMS (ESI): m/z calcd for C₁₄H₁₈NO₃ [M+H]⁺: 248.1287; found: 248.1275.

¹ S. Fustero, P. Bello, J. Miro, M. Sánchez-Roselló, M. A. Maestro, J. Gonzalez, C. del Pozo, Chem. Comm. 2013, 49, 1336.
A solution of CAN (6.20 g, 12.4 mmol) in H$_2$O (39 mL) was added drop-wise over 15 minutes to a stirred solution of S1 (1.50 g, 6.20 mmol) in MeCN (39 mL) cooled to 0 °C. After 2 hours stirring, the resulting solution was treated with 2N HCl to achieve pH 1. The aqueous phase was washed with EtOAc (3x) and basified to pH 10-12 by the addition of Na$_2$CO$_3$. The resulting suspension was extracted with CH$_2$Cl$_2$ (3x), dried over Na$_2$SO$_4$, filtered, and the solvents evaporated under reduced pressure to yield 570 mg of 1 (65% yield) as an orange oil without further purification. The spectroscopic data are in agreement with those previously reported in the literature.$^2$ HRMS (ESI): m/z calcd for C$_{7}$H$_{12}$NO$_{2}$ [M+H]$^{+}$: 142.0863; found: 142.0865.

**Synthesis of methyl 2-((tert-butoxycarbonyl)amino)-2-methylpent-4-ynoate (S2)**

![Chemical Structure](image)

Following an improved version of a reported procedure,$^3$ Boc$_2$O (465 mg, 2.13 mmol) was added to a solution of 1 (200 mg, 1.42 mmol) in THF (7 mL) and the resulting mixture was stirred at 70 °C overnight (in a sealed tube). Then, the solvent was evaporated under reduced pressure and the crude product was purified by flash column chromatography (silica gel; petroleum ether/EtOAc, 4:1) to yield 339 mg of S2 (99% yield) as a white solid. The spectroscopic data are in agreement with those previously reported in the literature for (S)-N-Boc-a-propargylalanine methyl ester.$^3$ HRMS (ESI): m/z calcd for C$_{12}$H$_{20}$NO$_{4}$ [M+H]$^{+}$: 242.1392; found: 242.1382.

---

$^2$ J. A. Bajgrowicz, B. Cossec, C. Pigiere, R. Jacquier, P. Viallefont, *Tetrahedron Letters* **1983**, 24, 3721.
$^3$ H. Sogawa, M. Shiotsuki, F. Sanda, *J. Polym. Sci. Part A: Polym. Chem.* **2012**, 50, 2008.
Synthesis of methyl 3-methyl-7-phenyl-1,2,3,4-tetrahydro-2,6-naphthyridine-3-carboxylate (2) and methyl 3-methyl-6-phenyl-1,2,3,4-tetrahydro-2,7-naphthyridine-3-carboxylate (3)

A solution of S2 (150 mg, 0.62 mmol) in DMF (3.0 mL) was added to a suspension of sodium hydride (60% in mineral oil, 30 mg, 0.74 mmol) in DMF (3.2 mL) cooled to 0 ºC. After 10 minutes stirring, propargyl bromide (80 wt. % in toluene, 0.138 mL, 1.24 mmol) was added and the mixture was warmed to room temperature and stirred for 4 hours. Then, the mixture was diluted with saturated aqueous solution of NH₄Cl and the aqueous layer was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried with Na₂SO₄, filtered, and the solvents were evaporated. The crude product was purified by flash column chromatography (silica gel; petroleum ether/EtOAc, 5:1) to yield 168 mg of methyl 2-(((tert-butoxycarbonyl)(prop-2-yn-1-yl)amino)-2-methylpent-4-ynoate (S3) (97% yield) as a colourless oil. Rₓ = 0.40 (petroleum ether/EtOAc; 5:1); ¹H NMR (400 MHz, CDCl₃) δ 1.43 (s, 9H), 1.70 (s, 3H), 1.99 (t, J = 2.6 Hz, 1H), 2.20 (t, J = 2.4 Hz, 1H), 2.73 (dd, J = 17.1, 2.5 Hz, 1H), 3.12 (d, J = 16.6 Hz, 1H), 3.69 (s, 3H), 4.02 (d, J = 18.5 Hz, 1H), 4.26 (br s, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 22.0, 27.0, 28.3, 34.1, 52.4, 62.5, 70.9, 71.1, 80.1, 80.9, 81.7, 154.3, 174.0; HRMS (ESI): m/z calcd for C₁₅H₂₂NO₄ [M+H]⁺: 280.1543; found: 280.1534.

CpCo(CO)₂ (6.4 mg, 0.036 mmol) and benzonitrile (0.05 mL, 0.48 mmol) were added to a solution of S3 (68 mg, 0.24 mmol) in toluene (2.4 mL), previously degassed with argon for
15 minutes, and the mixture was heated at 110 °C for 36 hours. Then, the solvent was removed under reduced pressure and the crude product was purified by column chromatography (silica gel; petroleum ether/EtOAc, gradient from 5:1 to 3:2). The resulting inseparable mixture of regioisomers (ca. 40:60 ratio as determined by $^1$H NMR) was dissolved in CH$_2$Cl$_2$ (1 mL) and TFA (0.5 mL) was then added to the solution. After 1 hour stirring the solvent was removed under reduced pressure. The crude product was dissolved in EtOAc (5 mL) and a saturated aqueous solution of NaHCO$_3$ (5 mL) was added and the mixture was stirred for 10 minutes. Then, the organic layer was separated, dried over Na$_2$SO$_4$, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silica gel; gradient from EtOAc:MeOH 1:0 to 9:1) to afford 20 mg of 2 (30% yield) and 18 mg of 3 (26% yield) both as a colourless oils.

Data of minor regioisomer (2):

$R_f$ = 0.21 (EtOAc): $^1$H NMR (400 MHz, CDCl$_3$) δ 1.48 (s, 3H), 2.37 (br s, 1H), 2.83 (d, $J$ = 16.7 Hz, 1H), 3.35 (d, $J$ = 16.7 Hz, 1H), 3.69 (s, 3H), 4.05 – 4.18 (m, 2H), 7.39 (ddd, $J$ = 7.3, 3.7, 1.3 Hz, 1H), 7.41 – 7.49 (m, 3H), 7.90 – 7.98 (m, 2H), 8.37 (s, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 26.6, 37.3, 42.6, 52.5, 57.9, 120.6, 126.9, 128.3, 128.8, 128.8, 139.4, 143.2, 147.8, 155.3, 175.9; HRMS (ESI): m/z calcd for C$_{17}$H$_{19}$N$_2$O$_2$ [M+H]$^+$: 283.1441; found: 283.1431.

Data of major regioisomer (3):

$R_f$ = 0.32 (EtOAc): $^1$H NMR (400 MHz, CDCl$_3$) δ 1.48 (s, 3H), 2.03 (br s, 1H), 2.80 (d, $J$ = 16.2 Hz, 1H), 3.33 (d, $J$ = 16.2 Hz, 1H), 3.68 (s, 3H), 4.08 (d, $J$ = 17.0 Hz, 1H), 4.19 (d, $J$ = 17.1 Hz, 1H), 7.34 – 7.41 (m, 2H), 7.41 – 7.48 (m, 2H), 7.86 – 7.97 (m, 2H), 8.43 (s, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 26.4, 34.7, 44.7, 52.6, 58.1, 117.8, 126.9, 127.8, 128.8, 129.0, 139.4, 143.3, 150.2, 155.1, 175.8; HRMS (ESI): m/z calcd for C$_{17}$H$_{19}$N$_2$O$_2$ [M+H]$^+$: 283.1441; found: 283.1431.

Synthesis of methyl 4-methyl-6-methylene-2-oxo-1,3-oxazinane-4-carboxylate (4)
A suspension of Ph$_3$PAuCl (2 mg, 5 mol%) and AgNTf$_2$ (1.6 mg, 5 mol%) in DCE (0.1 mL) was added drop-wise to a stirred solution of S2 (20 mg, 0.083 mmol) in DCE (1 mL) and the resulting solution was stirred at 40 ºC for 3 hours. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (silica gel; petroleum ether/EtOAc, 1:1) to afford 10 mg of 4 (65% yield) as a colourless oil. R$_f$ = 0.23 (petroleum ether/EtOAc, 1:1); mp 66 – 68 ºC; $^1$H NMR (400 MHz, CDCl$_3$) δ 1.50 (s, 3H), 2.57 (d, $J$ = 14.3 Hz, 1H), 2.82 (d, $J$ = 14.3 Hz, 1H), 3.78 (s, 3H), 4.38 (s, 1H), 4.79 (d, $J$ = 1.1 Hz, 1H), 6.31 (br s, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 25.5, 35.2, 53.4, 56.9, 96.3, 149.8, 150.4, 172.6; HRMS (ESI): m/z calcd for C$_8$H$_{12}$NO$_4$ [M+H]$^+$: 186.0761; found: 186.0764.

**Synthesis of methyl 5,6-dimethyl-7-oxo-4,5,6,7-tetrahydrobenzo[g][1,2,3]triazolo[1,5-a][1,5]diazocine-5-carboxylate (5)**

2-Azidobenzoyl chloride (120 mg, 0.66 mmol) and Et$_3$N (0.09 mL, 0.66 mmol) were added to a solution of 1 (62 mg, 0.44 mmol) in CH$_2$Cl$_2$ (2.2 mL) cooled to 0 ºC. After 30 minutes stirring, the mixture was diluted with saturated aqueous solution of NH$_4$Cl and the aqueous
layer was extracted with CH$_2$Cl$_2$ (3x). The organic layer was separated, dried over Na$_2$SO$_4$, filtered and the solvents were concentrated in vacuo. The crude product was purified by flash column chromatography (silica gel; petroleum ether/EtOAc, 2:1) to yield 104 mg of methyl 2-(2-azidobenzamido)-2-methylpent-4-ynoate (S4) (83% yield) as a white solid. R$_f$ = 0.33 (petroleum ether/EtOAc, 2:1); mp 115 – 117 ºC; $^1$H NMR (400 MHz, CDCl$_3$) δ 1.72 (s, 3H), 2.03 (t, J = 2.6 Hz, 1H), 3.08 (d, J = 2.6 Hz, 2H), 3.79 (s, 3H), 7.23 (dd, J = 13.4, 7.7 Hz, 2H), 7.51 (td, J = 7.9, 1.5 Hz, 1H), 8.13 (dd, J = 7.9, 1.4 Hz, 1H), 8.29 (br s, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 23.0, 26.8, 53.1, 59.3, 71.3, 118.6, 124.6, 125.3, 132.4, 132.8, 137.5, 163.8, 173.4; HRMS (ESI): m/z calcd for C$_{14}$H$_{14}$N$_4$NaO$_3$ [M+Na]$^+$: 309.0958; found: 309.0952.

Sodium hydride (60% in mineral oil, 12.0 mg, 0.30 mmol) was added to a solution of S4 (55.0 mg, 0.20 mmol) in DMF (1 mL) cooled to 0 ºC. After 10 min stirring, iodomethane (0.025 mL, 0.40 mmol) was added and the mixture was stirred for 2 hours. Then, the mixture was diluted with saturated aqueous solution of NH$_4$Cl and the aqueous layer was extracted with EtOAc (3x). The organic layer was separated, dried over Na$_2$SO$_4$, filtered and the solvents were concentrated in vacuo. The crude product was purified by flash column chromatography (silica gel; petroleum ether/EtOAc, 4:1) to yield 57 mg of methyl 2-(2-azido-N-methylbenzamido)-2-methylpent-4-ynoate (S5) (95% yield) as a white solid. R$_f$ = 0.24 (petroleum ether/EtOAc, 4:1); mp 94 – 96 ºC; $^1$H NMR (400 MHz, CDCl$_3$) δ 1.68 (s, 3H), 2.03 (s, 1H), 2.65 – 2.90 (br s, 1H), 3.00 (s, 3H), 3.51 (d, J = 17.2 Hz, 1H), 3.76 (s, 3H), 7.08 – 7.33 (m, 3H), 7.32 – 7.51 (m, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 21.9, 25.4, 34.5, 52.6, 62.0, 70.6, 80.5, 118.7, 125.2, 128.0, 128.9, 130.6, 136.7, 169.0, 173.4; HRMS (ESI): m/z calcd for C$_{15}$H$_{16}$N$_4$NaO$_3$ [M+Na]$^+$: 323.1115; found: 323.1108.

A solution of S5 (30 mg, 0.10 mmol) in toluene (2 mL) was degassed for 15 minutes with an argon purge. Cp*RuCl(COD) (3.8 mg, 10 mol%) was added and the mixture was stirred at 80 ºC for 4 hours. Then, the solvent was removed under reduced pressure and the crude
product was purified by flash column chromatography over silica gel (silica gel; EtOAc) to yield 16 mg of 5 (53% yield) as a white solid. \( R_f = 0.26 \) (EtOAc); mp 176 – 178 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 1.75 (s, 3H), 3.02 (s, 3H), 3.24 (d, \( J = 16.6 \) Hz, 1H), 3.45 (s, 3H), 3.89 (d, \( J = 16.5 \) Hz, 1H), 7.43 – 7.65 (m, 5H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \( \delta \) 29.1, 30.4, 32.0, 53.3, 64.0, 126.1, 130.0, 130.9, 131.6, 132.9, 133.2, 133.5, 133.8, 168.5, 173.1; HRMS (EI): \( m/z \) calcd for C\(_{15}\)H\(_{17}\)N\(_4\)O\(_3\) [M+H]\(^+\): 301.1295; found: 301.1288.

**Synthesis of methyl 2-acetamido-2-methylpent-4-ynoate (S6)**

![Synthesis of methyl 2-acetamido-2-methylpent-4-ynoate (S6)](image)

To a solution of 1 (50 mg, 0.35 mmol) in CH\(_2\)Cl\(_2\) (1 mL) cooled to 0 °C, was added acetyl chloride (0.037 mL, 0.53 mmol) and Et\(_3\)N (0.10 mL, 0.70 mmol) and the mixture warmed to room temperature and stirred for 16 hours. Saturated aqueous solution of NH\(_4\)Cl was added and the organic layer was separated. The aqueous layer was extracted with CH\(_2\)Cl\(_2\) (2x) and the combined organic layers were dried over Na\(_2\)SO\(_4\), filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silica gel; petroleum ether/EtOAc; 4:1) to afford 58 mg of S6 (89% yield) as a white solid. \( R_f = 0.35 \) (petroleum ether/EtOAc, 1:2); mp 100 – 102 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 1.53 (s, 3H), 1.95 – 1.99 (m, 4H), 2.87 – 2.99 (m, 2H), 3.72 (s, 3H), 6.43 (br s, 1H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \( \delta \) 22.8, 23.4, 26.3, 52.9, 58.5, 71.1, 79.6, 169.8, 173.5; HRMS (ESI): \( m/z \) calcd for C\(_9\)H\(_{13}\)NNaO\(_3\) [M+Na]\(^+\): 206.0788; found: 206.0778.

**Synthesis of methyl 2,6-dimethyl-4-oxo-1,2,3,4-tetrahydropyridine-2-carboxylate (6)**
To a stirred solution of S6 (20 mg, 0.109 mmol) in MeOH (2.3 mL), AuSPhos(MeCN)SbF$_6$ (4.8 mg, 5 mol%) was added and the resulting solution was heated at 50 ºC for 5 hours. Then, the solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (silica gel; EtOAc) to yield 15 mg of 6 (75% yield) as a white solid. $R_f = 0.20$ (EtOAc); mp 111 – 113 ºC; $^1$H NMR (400 MHz, CDCl$_3$) δ 1.50 (s, 3H), 2.00 (s, 3H), 2.49 (d, $J = 16.3$ Hz, 1H), 2.83 (d, $J = 16.3$ Hz, 1H), 3.76 (s, 3H), 4.97 (s, 1H), 5.14 (br s, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 21.5, 24.3, 44.0, 53.2, 60.5, 100.0, 160.6, 174.7, 190.6; HRMS (EI): m/z calcd for C$_9$H$_{14}$NO$_3$ [M+H]$^+$: 184.0968; found: 184.0967.

**Synthesis of methyl 4-(2-amino-3-methoxy-2-methyl-3-oxopropyl)isoxazole-3-carboxylate (7)**

Benzyl bromide (0.56 mL, 4.68 mmol) and DIPEA (0.82 mL, 4.68 mmol) were added to a solution of 1 (220 mg, 1.56 mmol) in MeCN (10 mL) and the reaction mixture was heated at 80 ºC overnight (in a sealed tube). Then, the solvent was removed in vacuo and the resulting residue was diluted in EtOAc. The organic layer was washed with saturated aqueous
solution of NaHCO₃, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica gel; petroleum ether/EtOAc; 9:1) to afford 347 mg of methyl 2-(dibenzylamino)-2-methylpent-4-ynoate (S7) (69% yield) as a colourless oil. \( R_f = 0.36 \) (petroleum ether/EtOAc; 9:1); \(^1\)H NMR (400 MHz, CDCl₃) \( \delta \) 1.52 (s, 3H), 2.10 (t, \( J = 2.7 \) Hz, 1H), 2.75 (qd, \( J = 16.8, 2.6 \) Hz, 2H), 3.73 (s, 3H), 3.86 (s, 4H), 7.11 – 7.16 (m, 2H), 7.18 – 7.24 (m, 4H), 7.31 – 7.36 (m, 4H); \(^13\)C NMR (101 MHz, CDCl₃) \( \delta \) 22.4, 28.2, 51.8, 54.9, 66.7, 71.3, 81.0, 126.7, 128.0, 128.5, 141.0, 174.3; HRMS (ESI): \( m/z \) calcd for \( \text{C}_{21}\text{H}_{24}\text{NO}_2 \) [M+H]⁺: 322.1807; found: 322.1818.

A solution of S7 (40 mg, 0.12 mmol) in DCE (1.2 mL) was degassed for 15 minutes with an argon purge. Cp*RuCl(COD) (10 mol%, 4.60 mg, 0.012 mmol), ethyl 2-chloro-2-(hydroxyimino)acetate (20 mg, 0.13 mmol) and Et₃N (0.021 mL, 0.15 mmol) were added and the mixture was stirred at 80 °C for 2 hours. Then, the solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (silica gel; petroleum ether/EtOAc, 6:1) to yield 30 mg of ethyl 4-(2-(dibenzylamino)-3-methoxy-2-methyl-3-oxopropyl)isoxazole-3-carboxylate (S8) (57% yield) as a colourless oil. \( R_f = 0.30 \) (petroleum ether/EtOAc, 6:1); \(^1\)H NMR (400 MHz, CDCl₃) \( \delta \) 1.27 (s, 3H), 1.41 (t, \( J = 7.1 \) Hz, 3H), 3.29 (d, \( J = 14.8 \) Hz, 1H), 3.41 (d, \( J = 14.8 \) Hz, 1H), 3.64 (s, 3H), 3.81 – 3.93 (m, 4H), 4.41 (q, \( J = 7.1 \) Hz, 2H), 7.10 – 7.17 (m, 2H), 7.17 – 7.27 (m, 8H), 8.38 (s, 1H); \(^13\)C NMR (101 MHz, CDCl₃) \( \delta \) 14.3, 21.1, 28.2, 51.8, 55.0, 62.1, 68.1, 116.3, 126.9, 128.2, 128.6, 140.8, 154.5, 159.5, 160.8, 174.7; HRMS (ESI): \( m/z \) calcd for \( \text{C}_{25}\text{H}_{29}\text{N}_2\text{O}_5 \) [M+H]⁺: 437.2071; found: 437.2066.

A solution of S8 (15 mg, 0.034 mmol) in MeOH (1.7 mL) was hydrogenated in an H-CUBE reactor (1 ml/min, Pd(OH)₂ 20% cartridge, full H₂, room temperature). The solvent was evaporated *in vacuo* and the crude product was purified by flash column chromatography (silica gel; EtOAc) to yield 6 mg of 7 (72% yield) as a white solid. \( R_f = 0.35 \) (EtOAc 100%); mp 173 – 175 °C; \(^1\)H NMR (400 MHz, CDCl₃) \( \delta \) 1.35 (s, 3H), 1.64 (br s, 2H), 3.03 (d, \( J = 14.6 \) Hz, 3H), 3.07 – 3.15 (m, 4H), 3.69 – 3.76 (m, 2H), 3.79 – 3.86 (m, 4H), 3.94 – 4.02 (m, 4H), 5.37 (t, \( J = 7.1 \) Hz, 2H), 7.09 – 7.16 (m, 2H), 7.17 – 7.27 (m, 8H), 8.39 (s, 1H); \(^13\)C NMR (101 MHz, CDCl₃) \( \delta \) 21.1, 28.2, 51.9, 55.0, 62.1, 68.1, 116.3, 126.9, 128.2, 128.6, 140.8, 154.5, 159.5, 160.8, 174.7; HRMS (ESI): \( m/z \) calcd for \( \text{C}_{25}\text{H}_{26}\text{N}_2\text{O}_5 \) [M+H]⁺: 437.2071; found: 437.2066.
Hz, 1H), 3.15 (d, J = 14.6 Hz, 1H), 3.71 (s, 3H), 3.97 (s, 3H), 8.45 (s, 1H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 26.5, 32.0, 52.6, 52.8, 58.0, 115.9, 154.5, 159.0, 161.4, 177.1; HRMS (EI): m/z calcd for C$_{16}$H$_{15}$N$_2$O$_5$ [M+H]$^+$: 243.0975; found: 243.0969.

Synthesis of methyl 2-amino-3-(1-(2-ethoxy-2-oxoethyl)-1H-1,2,3-triazol-5-yl)-2-methylpropanoate (8)

A solution of S2 (1.0 g, 4.14 mmol) and ethyl 2-azidoacetate (803 mg, 6.22 mmol) in toluene (24 mL) was degassed for 15 minutes with an argon purge. Cp*RuCl(COD) (38 mg, 0.1 mmol) was added and the mixture was stirred at 50 ºC for 1 hour. Then, the solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (silica gel; petroleum ether/EtOAc, gradient from 1:1 to 1:2) to yield 1.51 g of 2-((tert-butoxycarbonyl)amino)-3-(1-(2-ethoxy-2-oxoethyl)-1H-1,2,3-triazol-5-yl)-2-methylpropanoate (S9) (99% yield) as a white solid. $R_f = 0.25$ (petroleum ether/EtOAc, 1:1); mp 67 – 69 ºC; $^1$H NMR (400 MHz, CDCl$_3$) δ 1.27 (t, J = 7.1 Hz, 3H), 1.41 (s, 9H), 1.53 (s, 3H), 3.39 (d, J = 15.5 Hz, 1H), 3.53 (d, J = 15.5 Hz, 1H), 3.78 (s, 3H), 4.22 (q, J = 7.1 Hz, 2H), 5.13 (s, 2H), 5.27 (s, 1H), 7.74 (s, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 14.2, 24.3, 28.4, 29.3, 48.9, 53.2, 59.2, 62.4, 80.6, 133.5, 133.8, 154.7, 166.6, 173.7; HRMS (EI): m/z calcd for C$_{16}$H$_{27}$N$_4$O$_6$ [M+H]$^+$: 371.125; found: 371.1927.

TFA (10 mL) was added to a solution of S9 (1.51 g, 4.08 mmol) in CH$_2$Cl$_2$ (30 mL) and after 2 hours stirring the solvent was removed under reduced pressure. The crude product was dissolved in EtOAc and a saturated aqueous solution of NaHCO$_3$ was added and the mixture was stirred for 10 minutes. Then, the organic layer was separated, dried over Na$_2$SO$_4$, 17
filtered and concentrated in vacuo to afford 880 mg 8 (80% yield) as a white solid without further purification. $R_f = 0.22$ (EtOAc); mp 73 – 75 °C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.27 (t, $J = 7.1$ Hz, 3H), 1.38 (s, 3H), 1.73 (br s, 2H), 2.83 (d, $J = 14.9$ Hz, 1H), 3.15 (d, $J = 14.9$ Hz, 1H), 3.71 (s, 3H), 4.22 (q, $J = 7.1$ Hz, 2H), 5.20 – 5.48 (m, 2H), 7.48 (s, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 14.2, 27.0, 34.1, 49.5, 52.8, 58.3, 62.3, 133.9, 133.9, 166.9, 176.6; HRMS (EI): $m/z$ calcd for C$_{11}$H$_{18}$N$_4$NaO$_4$ [M+Na]$^+: 293.1220$; found: 293.1212.

**Synthesis of methyl 5-methyl-7-oxo-4,5,6,7-tetrahydrooxazolo[3,4-c]pyridine-5-carboxylate (9)**

A solution of S8 (15 mg, 0.034 mmol) in EtOH (1.7 mL) was hydrogenated in an H-CUBE reactor (1ml/min, Pd(OH)$_2$ 20% cartridge, full H$_2$, room temperature). The solvent was evaporated in vacuo in a warmed bath at 40 °C. The crude product was purified by flash column chromatography (silica gel; petroleum ether/EtOAc, 1:2) to yield 5 mg of 9 (69% yield) as a white solid. $R_f = 0.24$ (petroleum ether/EtOAc, 1:2); mp 174 – 176 °C; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 1.59 (s, 3H), 2.96 (dd, $J = 15.6$, 1.2 Hz, 1H), 3.32 (d, $J = 15.6$ Hz, 1H), 3.75 (s, 3H), 6.41 (br s, 1H), 8.38 (t, $J = 1.1$ Hz, 1H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 26.2, 28.4, 53.6, 61.0, 113.9, 153.4, 155.3, 158.3, 172.9; HRMS (ESI): $m/z$ calcd for C$_9$H$_{16}$N$_4$NaO$_4$ [M+Na]$^+: 233.0533$; found: 233.0526.

**Synthesis of methyl 5-methyl-7-oxo-5,6,7,8-tetrahydro-4H-[1,2,3]triazolo[1,5-d][1,4]diazepine-5-carboxylate (10)**
A stirred solution of 8 (200 mg, 0.74 mmol) in toluene (12 mL) was heated at 150 °C for 66 hours. Then, the solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (silica gel; EtOAc/MeOH, gradient from 1:0 to 9:1) to afford 140 mg of 10 (84% yield) as a white solid. \( R_f = 0.18 \) (EtOAc 100%); mp 147 – 149 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 1.54 (s, 3H), 3.34 (d, \( J = 15.8 \) Hz, 1H), 3.56 (d, \( J = 15.7 \) Hz, 1H), 3.70 (s, 3H), 5.28 (m, 2H), 6.90 (br s, 1H), 7.54 (s, 1H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \( \delta \) 27.4, 31.0, 52.7, 53.7, 60.8, 131.9, 133.6, 165.2, 172.1; HRMS (EI): \( m/z \) calcd for \( \text{C}_9\text{H}_{13}\text{N}_4\text{O}_3 \) [M+H\(^+\)]\(^\cdot\) 225.0982; found: 225.0978.

**Synthesis of methyl 2-amino-2-methyl-3-(1-phenyl-1H-1,2,3-triazol-5-yl)propanoate (11)**

A solution of S2 (50 mg, 0.20 mmol) and azidobenzene (0.5 M in tert-butyl methyl ether, 0.62 mL, 0.31 mmol) in toluene (1 mL) was degassed for 15 minutes with an argon purge. \( \text{Cp}^*\text{RuCl(COD)} \) (3.7 mg, 0.01 mmol) was added and the mixture was stirred at 80 °C for 3 hours. Then, the solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (silica gel; petroleum ether/EtOAc, 1:1) to yield 46 mg of methyl 2-(((tert-butoxycarbonyl)amino)-2-methyl-3-(1-phenyl-1H-1,2,3-triazol-5-yl)propanoate (S10) (64% yield) as a colourless oil. \( R_f = 0.24 \) (petroleum ether/EtOAc, 1:1); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 1.34 (s, 3H), 1.40 (s, 9H), 3.45 (d, \( J = 15.5 \) Hz, 1H), 3.52 – 3.71
TFA (0.4 mL) was added to a solution of S10 (46 mg, 0.13 mmol) in CH$_2$Cl$_2$ (1 mL) and after 2 hours stirring the solvent was removed under reduced pressure. The crude product was dissolved in EtOAc and a saturated aqueous solution of NaHCO$_3$ was added and the mixture was stirred for 10 minutes. Then, the organic layer was separated, dried over Na$_2$SO$_4$, filtered and concentrated in vacuo. The crude product was puriﬁed by ﬂash column chromatography (silica gel; EtOAc/MeOH, from gradient 1:0 to 20:1) to afford 21 mg 11 (62% yield) as a white solid without further puriﬁcation. $R_f = 0.19$ (EtOAc); mp 65 – 67 °C; $^1$H NMR (400 MHz, CDCl$_3$) δ 1.28 (s, 3H), 1.65 (s, 2H), 2.96 (d, $J = 15.0$ Hz, 1H), 3.20 (d, $J = 15.0$ Hz, 1H), 3.64 (s, 3H), 7.45 – 7.50 (m, 2H), 7.50 – 7.60 (m, 3H), 7.63 (s, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 26.8, 34.2, 52.7, 58.0, 126.2, 129.6, 129.8, 133.4, 133.7, 136.3, 176.7; HRMS (El): m/z calcd for C$_{13}$H$_{17}$N$_4$O$_2$ [M+H]$^+$: 261.1346; found: 261.1336.

Synthesis of methyl 2-amino-2-methyl-3-(1-phenyl-1H-1,2,3-triazol-4-yl)propanoate (12)

CuSO$_4$·5H$_2$O (6.47 mg, 5 mol%) and sodium ascorbate (31 mg, 0.155 mmol) were added to a solution of S2 (125 mg, 0.52 mmol) and azidobenzene (0.5 M in tert-butyl methyl ether, 2.08 mL, 1.04 mmol) in a mixture 1:1 of t-BuOH:H$_2$O (2 mL) and the reaction stirred overnight. Then, the reaction was concentrated in vacuo and the aqueous layer was extracted with EtOAc (3x). The combined organic layer was washed with 5% aqueous
solution of NH$_4$OH, dried over Na$_2$SO$_4$, filtered and concentrated \textit{in vacuo}. The crude product was purified by flash column chromatography (silica gel; petroleum ether/EtOAc, 2:1) to yield 177 mg of methyl 2-((\textit{tert}-butoxycarbonyl)amino)-2-methyl-3-(1-phenyl-1H-1,2,3-triazol-4-yl)propanoate (S11) (95\% yield) as white solid. $R_f = 0.23$ (petroleum ether/EtOAc, 2:1); mp 99 – 101 \textcelsius; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.43 (s, 9H), 1.60 (s, 3H), 3.45 (d, $J = 14.4$ Hz, 1H), 3.52 (d, $J = 14.6$ Hz, 1H), 3.79 (s, 3H), 5.44 (br s, 1H), 7.42 (t, $J = 7.4$ Hz, 1H), 7.51 (t, $J = 7.7$ Hz, 2H), 7.70 (d, $J = 7.8$ Hz, 2H), 7.75 (s, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 23.7, 28.3, 32.6, 52.8, 59.2, 79.7, 120.3, 120.8, 128.6, 129.7, 137.0, 143.6, 154.0, 174.3; HRMS (ESI): $m/z$ calcd for C$_{18}$H$_{25}$N$_4$O$_4$ [M+H]$^+$: 361.1870; found: 361.1868.

TFA (0.4 mL) was added to a solution of S11 (50 mg, 0.14 mmol) in CH$_2$Cl$_2$ (1 mL) and after 2 hours stirring the solvent was removed under reduced pressure. The crude product was dissolved in EtOAc and a saturated aqueous solution of NaHCO$_3$ was added and the mixture was stirred for 10 minutes. Then, the organic layer was separated, dried over Na$_2$SO$_4$, filtered and concentrated \textit{in vacuo}. The crude product was purified by flash column chromatography (silica gel; EtOAc/MeOH, 10:2) to yield 36 mg 12 (98\% yield) as a white solid. $R_f = 0.36$ (EtOAc/MeOH, 10:2); mp 72 – 74 \textcelsius; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.44 (s, 3H), 1.89 (br s, 2H), 3.05 (d, $J = 14.4$ Hz, 1H), 3.28 (d, $J = 14.4$ Hz, 1H), 3.73 (s, 3H), 7.47 – 7.53 (m, 1H), 7.67 – 7.78 (m, 2H), 7.67 – 7.78 (m, 2H), 7.83 (s, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 26.9, 36.8, 52.6, 58.1, 120.5, 120.7, 128.7, 129.8, 137.2, 144.2, 177.4; HRMS (EI): $m/z$ calcd for C$_{13}$H$_{17}$N$_4$O$_2$ [M+H]$^+$: 261.1346; found: 261.1346.

\textbf{Synthesis of 2-(4-amino-5-methoxy-4-methyl-5-oxopentyl)benzoic (13)}
A solution of S2 (500 mg, 2.1 mmol) in DMF (12 mL) was added over a period of 4 hours to a mixture of PdCl₂(PPh₃)₂ (74 mg, 5 mol%), CuI (40 mg, 10 mol%), Et₃N (1.48 mL), and benzyl 2-iodobenzoate (1.08 g, 3.18 mmol) in degassed DMF (25 mL). After 4 hours, the reaction mixture was diluted with EtOAc and washed with saturated aqueous solution of NaHCO₃ and brine. The organic layer was dried over Na₂SO₄, filtered and the solvents were removed in vacuo. The crude product was purified by flash column chromatography (silica gel; petroleum ether/EtOAc, 4:1) to yield 710 mg of benzyl 2-(4-((tert-butoxycarbonyl)amino)-5-methoxy-4-methyl-5-oxopent-1-yn-1-yl)benzoate (S12) (75% yield). Rf = 0.36 (petroleum ether/EtOAc, 3:1); mp 74 – 76 ºC; ¹H NMR (400 MHz, CDCl₃) δ 1.43 (s, 9H), 1.61 (s, 3H), 2.93 (d, J = 17.1 Hz, 1H), 3.20 (d, J = 17.1 Hz, 1H), 3.77 (s, 3H), 5.37 (q, J = 12.5 Hz, 2H), 5.72 (br s, 1H), 7.27 – 7.49 (m, 7H), 7.51 (d, J = 7.2 Hz, 1H), 7.95 (d, J = 7.3 Hz, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 23.4, 28.4, 28.4, 52.7, 58.7, 67.0, 79.9, 82.1, 91.1, 124.3, 127.7, 128.3, 128.4, 128.7, 130.4, 131.8, 131.9, 134.3, 136.0, 154.9, 165.9, 173.9 (two carbon signals overlap at 28.4); HRMS (ESI): m/z calcd for C₂₆H₂₅NNaO₆ [M+Na]+: 474.1887; found: 474.1877.

TFA (0.80 mL) was added to a solution of S12 (75 mg, 0.167 mmol) in CH₂Cl₂ (1.6 mL) and after 2 hours stirring the solvent was removed under reduced pressure. The crude product was dissolved in EtOAc and a saturated aqueous solution of NaHCO₃ was added and the mixture was stirred for 10 minutes. Then, the organic layer was separated, dried over Na₂SO₄, filtered and concentrated in vacuo. The crude product was purified by flash column
chromatography (silica gel; petroleum ether/EtOAc, 1:2) to afford 48 mg benzyl 2-(4-amino-5-methoxy-4-methyl-5-oxopent-1-yn-1-yl)benzoate (S13) (82% yield) as a colourless oil. \( R_f = 0.22 \) (petroleum ether/EtOAc, 1:2); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 1.44 (s, 3H), 2.28 (br s, 2H), 2.68 (d, \( J = 16.7 \) Hz, 1H), 2.89 (d, \( J = 16.7 \) Hz, 1H), 3.74 (s, 3H), 5.35 (s, 2H), 7.28 – 7.46 (m, 7H), 7.50 (dd, \( J = 7.7, 0.9 \) Hz, 1H), 7.93 (dd, \( J = 7.9, 0.9 \) Hz, 1H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \( \delta \) 26.2, 32.4, 52.6, 67.0, 82.3, 91.1, 124.1, 127.7, 128.3, 128.4, 128.7, 130.4, 131.8, 131.8, 134.4, 136.0, 165.8, 176.5; HRMS (ESI): \( m/z \) calcd for C\(_{21}\)H\(_{22}\)NO\(_4\) [M+H]\(^+\): 352.1543; found: 352.1530.

Pd(OH)\(_2\) (10% wt, 27 mg, 0.19 mmol) was added to a degassed solution of S13 (65 mg, 0.19 mmol) in MeOH (3.8 mL) and the mixture was stirred under H\(_2\) atmosphere (1 atm) for 8 hours. Then, the mixture was filtered through celite and the filtrate was concentrated \textit{in vacuo} to afford 40 mg of 13 (80% yield) as a colourless oil without further purification. \(^1\)H NMR (400 MHz, MeOD) \( \delta \) 1.41 – 1.55 (m, 4H), 1.62 – 1.79 (m, 1H), 1.79 – 2.01 (m, 2H), 2.89 – 3.00 (m, 2H), 3.75 (s, 3H), 7.24 (t, \( J = 7.1 \) Hz, 2H), 7.40 (t, \( J = 7.1 \) Hz, 1H), 7.86 (d, \( J = 7.2 \) Hz, 1H); \(^{13}\)C NMR (101 MHz, MeOD) \( \delta \) 22.6, 26.8, 34.9, 38.2, 53.9, 61.1, 127.4, 131.1, 132.1, 132.2, 133.2, 144.2, 170.8, 172.6; HRMS (ESI): \( m/z \) calcd for C\(_{14}\)H\(_{20}\)NO\(_4\) [M+H]\(^+\): 266.1387; found: 266.1377.

**Synthesis of tert-butyl (1-hydroxy-2-methylpent-4-yn-2-yl)carbamate (S14)**

![Chemical structure](image)

To a solution of S2 (1.62 g, 6.70 mmol) in THF (30 mL) at 0 °C was added LiBH\(_4\) (438 mg, 20.00 mmol) and the reaction stirred overnight. Then, the reaction mixture was quenched with H\(_2\)O and extracted with EtOAc (3x). The combined organics were dried over Na\(_2\)SO\(_4\),
filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silica gel; petroleum ether/EtOAc, 3:1) to afford 1.36g of S14 (96%) as a white solid. \( R_f = 0.35 \) (petroleum ether/EtOAc, 4:1); \(^1^H\) NMR (400 MHz, CDCl\(_3\)) \( \delta 1.32 \) (s, 3H), \( 1.46 \) (s, 9H), \( 2.07 \) (t, \( J = 2.7 \) Hz, 1H), \( 2.48 \) (dd, \( J = 16.8, 2.6 \) Hz, 1H), \( 2.72 – 2.78 \) (m, 1H), \( 3.70 \) (s, 2H), \( 4.90 \) (s, 1H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \( \delta 22.6, 26.7, 28.3, 55.9, 69.1, 71.2, 80.1, 80.2, 156.0 \); HRMS (ESI): \( m/z \) calcd for C\(_{11}\)H\(_{18}\)NO\(_3\) [M+H]\(^+\): 214.1443; found 214.1432.

**Synthesis of tert-butyl (6-methyl-2-phenyl-3,5,6,7,9,9a-hexahydro-2H-oxepino[4,3-e][1,2]oxazin-6-yl)carbamate (14)**

To a solution of S14 (40 mg, 0.188 mmol) in DMF (2 mL) at 0 °C was added sodium hydride (60% dispersion in mineral oil, 8.2 mg, 0.206 mmol). After 15 minutes, allyl bromide (45.5 uL, 0.376 mmol) was added and the reaction stirred for 90 minutes. Then, the reaction was diluted with H\(_2\)O and extracted with EtOAc (2x). The combined organic layers were dried over Na\(_2\)SO\(_4\), filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silica gel; petroleum ether/ EtOAc, 3:2) to give 28 mg of tert-butyl (1-(allyloxy)-2-methylpent-4-yn-2-yl)carbamate (S15) (59%) as a colourless oil. \( R_f = 0.54 \) (petroleum ether/EtOAc, 9:1); \(^1^H\) NMR (400 MHz, CDCl\(_3\)) \( \delta 1.41 \) (s, 3H), \( 1.45 \) (s, 9H), \( 2.01 \) (t, \( J = 2.7 \) Hz, 1H), \( 2.59 \) (dd, \( J = 16.7, 2.7 \) Hz, 1H), \( 2.76 – 2.86 \) (m, 1H), \( 3.45 \) (d, \( J = 9.1 \) Hz,
1H), 3.60 (d, J = 9.1 Hz, 1H), 4.03 (d, J = 5.6 Hz, 2H), 4.87 (s, 1H), 5.20 (dd, J = 10.4, 1.3 Hz, 1H), 5.29 (dt, J = 17.2, 1.5 Hz, 1H), 5.91 (ddt, J = 16.0, 10.8, 5.6 Hz, 1H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 21.5, 26.3, 28.4, 54.6, 70.5, 72.3, 74.0, 79.2, 80.7, 117.0, 134.6, 154.7; HRMS (ESI): \(m/z\) calcd for C\(_{14}\)H\(_{23}\)NO\(_3\)Na [M+H]\(^+\): 276.1576, found 276.1570.

A solution of S15 (150 mg, 0.592 mmol) in CH\(_2\)Cl\(_2\) (10 mL) was degassed with an argon purge. Grubbs-II (50 mg, 0.0592 mmol) was added to the reaction was degassed with ethylene and stirred under this atmosphere for 18 hours. Then, the reaction was concentrated \emph{in vacuo} and purified by flash column chromatography (silica gel; petroleum ether/EtOAc, 19:1) to give 60 mg of tert-butyl (3-methyl-5-vinyl-2,3,4,7-tetrahydrooxepin-3-yl)carbamate (S16) (40%) as a colourless oil. \(R_f\) = 0.3 (petroleum ether/EtOAc, 8:1); \(^{1}\)H (400 MHz, CDCl\(_3\)) \(\delta\) 1.37 (s, 3H), 1.38 (s, 9H), 2.39 (d, J = 15.0 Hz, 1H), 3.18 (d, J = 14.0 Hz, 1H), 3.49 (d, J = 12.3 Hz, 1H), 3.90 (d, J = 12.3 Hz, 1H), 4.12 (dd, J = 15.2, 4.9 Hz, 1H), 4.28 (dd, J = 15.0, 6.1 Hz, 1H), 4.88 (bs, 1H), 5.04 (d, J = 10.9 Hz, 1H), 5.33 (d, J = 17.4 Hz, 1H), 5.86 (t, J = 5.5 Hz, 1H), 6.31 (dd, J = 17.4, 10.9 Hz, 1H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 23.4, 28.4, 35.5, 52.8, 69.1, 78.9, 81.6, 113.8, 129.9, 139.5, 140.0, 154.9; HRMS (ESI): \(m/z\) calcd for C\(_{14}\)H\(_{23}\)NO\(_3\)Na [M+H]\(^+\): 276.1576, found 276.1585.

To a solution of S16 (60 mg, mmol) in toluene (2.5 mL) was added nitrosobenzene (51 mg, mmol) and the reaction heated to 110 °C for 4 hours. Then, the reaction was concentrated under reduced pressure to give a mixture of diastereomers (dr ca. 46:36:10:0 determined by \(^{1}\)H NMR). The major isomer was isolated by flash column chromatography (silica gel; petroleum ether/EtOAc 22:3) to give 26 mg of 14 (31%) as a yellow oil.\(^4\) Data for isolated diastereomer 14: \(R_f\) = 0.15 (petroleum ether/EtOAc 22:3); \(^{1}\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 1.29 (s, 3H), 1.44 (s, 9H), 2.62 – 2.75 (m, 2H), 3.27 (d, J = 12.7 Hz, 1H), 3.62 (dd, J = 11.4, 9.5 Hz, 1H), 3.99 (dd, J = 11.4, 6.6 Hz, 2H), 4.23 – 4.31 (m, 2H), 4.48 – 4.56 (m, 1H), 4.76 (s, 1H), 5.70 (d, J = 2.2 Hz, 1H), 6.9 – 6.96 (m, 1H), 7.03 (dd, J = 8.7, 1.0 Hz, 2H), 7.26 – 7.29

\(^4\) The diastereomeric ratio was determined by \(^{1}\)H NMR. Only three out of the four possible diastereomers were detected by \(^{1}\)H NMR.
(m, 2H); $^{13}$C (101 MHz, CDCl$_3$) δ 22.3, 28.4, 45.7, 55.1, 61.8, 67.1, 72.0, 78.2, 80.9, 115.7, 121.8, 123.2, 129.0, 133.1, 147.6, 154.7; HRMS (ESI): $m/z$ calcd for C$_{20}$H$_{28}$N$_2$O$_4$Na [M+H]$^+$: 383.1941, found 383.1931.

**Synthesis of N-(1-hydroxy-2-methylpent-4-yn-2-yl)acetamide (S17)**

To a solution of S6 (810 mg, 4.42 mmol) in THF (44 mL) at 0 °C was added LiBH$_4$ (192 mg, 8.8 mmol) and the reaction stirred for 16 hours. Then, the reaction was quenched with water and extracted with EtOAc (3x). The combined organic extracts were washed with brine, dried over Na$_2$SO$_4$, filtered and concentrated in vacuo to give 568 mg of S17 (83%) as a white solid without further purification. $R_f = 0.22$ (petroleum ether/EtOAc, 4:1); mp 107 – 109 °C; $^1$H NMR (400 MHz, CDCl$_3$) δ 1.35 (s, 3H), 2.05 (s, 3H), 2.10 (t, $J = 2.6$ Hz, 1H), 2.45 (dd, $J = 16.9$, 2.6 Hz, 1H), 2.83 (dd, $J = 16.9$, 2.6 Hz, 1H), 3.69 (d, $J = 5.6$ Hz, 2H), 4.70 (d, $J = 5.8$ Hz, 1H), 5.77 (s, 1H); $^{13}$C (101 MHz, CDCl$_3$) δ 22.7, 24.0, 26.7, 57.6, 69.1, 71.5, 80.0, 171.3; HRMS (ESI): $m/z$ calcd for C$_8$H$_{14}$NO$_2$ [M+H]$^+$: 156.1019, found 156.1019.

**Synthesis of N-(4,9-dimethyl-7-phenyl-1,3,4,5-tetrahydrooxepino[3,4-c]pyridin-4-yl)acetamide (15)**
A solution of S17 (150 mg, 0.965 mmol) in DMF (9.6 mL) was cooled to 0 °C before sodium hydride (60% dispersion in mineral oil, 42 mg, 1.06 mmol) was added. After 20 minutes 1-bromo-2-butyne (93 uL, 1.06 mmol) was added and the reaction was stirred for 3 hours warming to room temperature. Then, NH₄Cl (sat. aq) was added and the reaction mixture was extracted with EtOAc (3x). The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silica gel; petroleum ether/EtOAc, 3:2) to give 164 mg of N-(1-(but-2-yn-1-yloxy)-2-methylpent-4-yn-2-yl)acetamide (S18) (82%) as a colourless oil. Rᵢ = 0.22 (petroleum ether/EtOAc, 3:2); ¹H (400 MHz, CDCl₃) δ 1.47 (s, 3H), 1.88 (t, J = 2.3 Hz, 3H), 1.97 (s, 3H), 2.01 (t, J = 2.7 Hz, 1H), 2.64 (dd, J = 16.7, 2.7 Hz, 1H), 2.94 (dd, J = 16.7, 2.7 Hz, 1H), 3.54 (d, J = 9.2 Hz, 1H), 3.72 (d, J = 9.2 Hz, 1H), 4.16 (m, J = 2.3 Hz, 2H), 5.70 (s, 1H); ¹³C (101 MHz, CDCl₃) δ 3.6, 21.1, 24.4, 25.9, 55.4, 59.2, 70.6, 73.5, 74.9, 80.6, 82.9, 170.1. HRMS (ESI): m/z calcd for C₁₂H₁₇NO₂Na [M+Na]⁺: 230.1152, found 230.1146.

CpCo(CO)₂ (96 uL, 0.540 mmol) and benzonitrile (104 uL, 1.544 mmol) and) were added to a solution of S18 (80 mg, 0.386 mmol) in toluene (3.8 mL) previously degassed with an argon purge, and the heated to 110 °C for 48 hours (in a sealed tube). Them, the reaction was cooled to room temperature and the solvents removed in vacuo. The crude product was purified by flash column chromatography (silica gel; petroleum ether/EtOAc, 7:3) 16 mg of 15 (22%) as a white solid (based on 39% recovered unreacted starting material). Data for 15: Rᵢ = 0.12 (petroleum ether/EtOAc, 1:1); mp 147 –151 °C; ¹H NMR (500 MHz, CDCl₃) δ 1.46 (s, 3H), 1.65 (s, 3H), 2.67 (s, 3H), 3.04 (d, J = 14.2 Hz, 1H), 3.64 (d, J = 12.3 Hz, 1H), 3.79 (dd, J = 14.3, 2.0 Hz, 1H), 3.98 (dd, J = 12.3, 2.0 Hz, 1H), 4.55 (d, J = 14.0 Hz, 1H), 5.13 (d, J = 14.0 Hz, 1H), 5.49 (s, 1H), 7.37 – 7.41 (m, 1H), 7.41 – 7.48 (m, 3H), 7.97 (dt, J = 8.3, 1.8 Hz, 2H); ¹³C NMR (126 MHz, CDCl₃) δ 22.6, 23.9, 29.7, 43.5, 54.0, 69.8, 83.0, 121.0, 126.9, 128.7, 128.9, 130.4, 139.1, 148.1, 154.8, 156.2, 170.2; HRMS (ESI): m/z calcd for C₁₉H₂₃N₂O₂ [M+H]⁺: 311.1760, found 311.1764.
Synthesis of \(\text{cis-N-(4,9-dimethyl-8,10-dioxo-3,4,5,7,7a,8,9,10,10a,10b-decahydro-1\text{-}H-oxepino[3,4-\text{e}]	ext{-}isoindol-4-yl)acetamide (16)}\)

To a solution of \(\text{S17} \) (250 mg, 1.61 mmol) in DMF (17.8 mL) at 0 °C was added sodium hydride (60% dispersion in mineral oil, 70 mg, 1.77 mmol). After 15 minutes allyl bromide (153 uL, 1.77 mmol) was added and the reaction was stirred for 3 hours. Then, \(\text{NH}_4\text{Cl} \) (sat. aq.) was added and the reaction mixture was extracted with EtOAc (3x). The combined organic extracts were washed with brine, dried over \(\text{Na}_2\text{SO}_4\), filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silica gel; petroleum ether/EtOAc, 3:2) to give 276 mg of \(\text{N-(1-(allyloxy)-2-methylpent-4-yn-2-yl)acetamide (S19)} \) (88%) as a colourless oil. \(R_f = 0.25 \) (petroleum ether/EtOAc, 3:2); \(^1\text{H} \) NMR (400 MHz, CDCl\(_3\)) \(\delta \) 1.46 (s, 3H), 1.96 (s, 3H), 2.01 (t, \(J = 2.7 \) Hz, 1H), 2.64 (dd, \(J = 16.7, 2.7 \) Hz, 1H), 2.92 (dd, \(J = 16.7, 2.7 \) Hz, 1H), 3.47 (d, \(J = 9.2 \) Hz, 1H), 3.66 (d, \(J = 9.2 \) Hz, 1H), 4.03 (d, \(J = 5.6 \) Hz, 2H), 5.21 (dd, \(J = 10.4, 1.3 \) Hz, 1H), 5.29 (dt, \(J = 17.3, 1.5 \) Hz, 1H), 5.69 (s, 1H), 5.91 (ddt, \(J = 16.0, 10.6, 5.6 \) Hz, 1H); \(^{13}\text{C} \) NMR (101 MHz, CDCl\(_3\)) \(\delta \) 21.2, 24.4, 25.9, 55.6, 70.6, 72.3, 73.8, 80.6, 117.2, 134.4, 170.1; HRMS (ESI): \(m/z \) calcd for \(\text{C}_{11}\text{H}_{18}\text{NO}_2 [\text{M+H}]^+: 196.1329, \) found 196.1332.

A solution of \(\text{S19} \) (240 mg, 1.18 mmol) in CH\(_2\)Cl\(_2\) (22.8 mL) was degassed with an argon purge for 15 minutes. Grubbs-II (100 mg, 0.118 mmol) was added and the reaction was
degassed with ethylene and stirred under this atmosphere for 18 hours. Then, the reaction was concentrated in vacuo and purified by flash column chromatography (silica gel; petroleum ether/EtOAc, 1:1) to give 120 mg of N-(3-methyl-5-vinyl-2,3,4,7-tetrahydrooxepin-3-yl)acetamide (S20) (52%). $R_f = 0.22$ (petroleum ether/EtOAc, 2:3); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.46 (s, 3H), 1.89 (s, 3H), 2.43 (d, $J = 15.0$ Hz, 1H), 3.30 (d, $J = 15.0$ Hz, 1H), 3.52 (d, $J = 12.4$ Hz, 1H), 3.99 (d, $J = 12.3$ Hz, 1H), 4.09 – 4.23 (m, 1H), 4.32 (dd, $J = 15.2$, 6.2 Hz, 1H), 5.09 (d, $J = 10.8$ Hz, 1H), 5.3 – 5.39 (m, 1H), 5.69 (br s, 1H), 5.88 (t, $J = 5.2$ Hz, 1H), 6.33 (dd, $J = 17.4$, 10.8 Hz, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 23.2, 24.3, 35.6, 53.8, 69.1, 81.4, 114.1, 129.7, 139.5, 140.0, 170.2; HRMS (ESI): m/z calcd for C$_{11}$H$_{17}$NO$_2$Na $[M^{+}Na]^+$: 218.1152, found 218.1146.

To a solution of S20 (45 mg, 0.230 mmol) in toluene (2.3 mL) was added N-methylmaleimide (51 mg, 4.62 mmol) and the reaction heated to 110 $^\circ$C for 5 hours. Then, the reaction was cooled to room temperature and concentrated in vacuo to give a mixture of diastereomers (dr = ca. 85:15 determined by $^1$H NMR). The major diastereomer was isolated by flash column chromatography (silica gel, EtOAc) to give 49 mg of 16 (70%) as a white solid. $R_f = 0.012$ (EtOAc); mp 134 – 137 $^\circ$C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.33 (s, 3H), 1.86 (s, 3H), 2.1 – 2.19 (m, 1H), 2.37 (d, $J = 14.4$ Hz, 1H), 2.57 – 2.64 (m, 1H), 2.68 – 2.75 (m, 1H), 2.92 (s, 3H), 3.02 – 3.08 (m, 2H), 3.16 (t, $J = 7.7$ Hz, 1H), 3.30 (d, $J = 12.5$ Hz, 1H), 3.87 (dd, $J = 12.5$, 2.2 Hz, 1H), 4.18 – 4.3 (m, 2H), 5.53 (s, 1H), 5.71 – 5.78 (m, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 22.0, 24.0, 24.9, 25.0, 40.6, 41.5, 42.7, 43.8, 56.7, 72.6, 81.4, 125.4, 139.6, 169.8, 178.0, 179.5; HRMS (ESI): m/z calcd for C$_{16}$H$_{23}$N$_2$O$_4$ $[M^{+}]^+$: 307.1658, found 307.1663.

**Synthesis of tert-butyl (3-methyl-5-methylene-2-oxotetrahydrofuran-3-yl)carbamate (17)**
To a stirred solution of S2 (150 mg, 1.06 mmol) in a mixture 2:1 of THF:H2O (9 mL), Boc2O (695 mg, 3.18 mmol) and a solution of 10% aqueous solution of NaOH (1 mL) were added. The mixture was stirred at room temperature overnight and then the organic solvent was removed under reduced pressure. The aqueous layer was washed with EtOAc (3x), acidified with 1N HCl (pH = 2-3) and extracted with EtOAc (3x). The combined organic layers were dried over Na2SO4, filtered and concentrated in vacuo to yield 186 mg of 2-((tert-butoxycarbonyl)amino)-2-methylpent-4-ynoic acid (S21) (77% yield) as a white solid without further purification.

To a stirred solution of S21 (24 mg, 0.105 mmol) in a mixture 1:1 of t-BuOH:H2O (2 mL), CuBr (4.5 mg, 10 mol%) was added. The resulting mixture was stirred for 6 hours, diluted with water, and extracted with EtOAc (3x). The organic layers were washed twice with brine, dried over Na2SO4, and evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel; petroleum ether/EtOAc, 4:1) to afford 22 mg of 17 (92% yield) as a white solid. Rf = 0.32 (petroleum ether/EtOAc, 4:1); mp 119 – 121 ºC; 1H NMR (400 MHz, CDCl3) δ 1.43 (s, 9H), 1.46 (s, 3H), 2.77 (dt, J = 16.0, 1.0 Hz, 1H), 3.20 – 3.55 (m, 1H), 4.35 (td, J = 2.5, 1.1 Hz, 1H), 4.77 – 4.80 (m, 1H), 5.04 (s, 1H); 13C NMR (101 MHz, CDCl3) δ 23.6, 28.3, 38.9, 56.8, 81.0, 90.1, 152.4, 154.5, 175.8; HRMS (EI): m/z calcd for C11H17KNO4 [M+K]+: 266.0791; found: 266.0795.

**Synthesis of tert-butyl (3-methyl-3,4-dihydro-2H-pyran-3-yl)carbamate (18)**
A solution of **S14** (19 mg, 0.0890 mmol), N-hydroxysuccinimide (5 mg, 0.0445 mmol), tetrabutylammonium hexafluorophosphonate (17.3 mg, 0.0445 mmol) and NaHCO₃ (3.80 mg, 0.0270 mmol) in DMF (1 mL) was degassed with an argon purge for 15 minutes. CpRu(PPh₃)₂Cl (6 mg, 0.024 mmol) and PPh₃ (2.10 mg, 0.008 mmol) were added and the reaction heated to 80 ºC for 56 hours (in a sealed tube). Then, the reaction was cooled to room temperature and filtered through celite, washing with EtOAc. The filtrate was washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica gel; petroleum ether/EtOAc 3:2) to give 9.1 mg of **18** (47%) as a colourless oil. \( R_f = 0.39 \) (petroleum ether/EtOAc 19:1); \(^1\)H NMR (400 MHz, CDCl₃) 1.37 (s, 3H), 1.43 (s, 9H), 1.97 (d, \( J = 17.2 \) Hz, 1H), 2.28 (d, \( J = 16.9 \) Hz, 1H), 3.56 (d, \( J = 11.0 \) Hz, 1H), 4.04 (d, \( J = 10.16 \) Hz, 1H), 4.66 – 4.63 (m, 2H), 6.35 (d, \( J = 5.9 \) Hz, 1H); \(^{13}\)C NMR (101 MHz, CDCl₃) 22.8, 28.4, 32.5, 48.6, 70.8, 79.2, 98.6, 143.2, 154.8; HRMS (EI): \( m/z \) calcd for C₁₁H₁₉NO₃Na [M+Na]⁺: 236.1257, found 236.1250.

**Synthesis of methyl 2-methyl-2-(1H-pyrrol-1-yl)pent-4-ynoate (19)**

NaOAc (97 mg, 1.19 mmol) was added to a stirred solution of **1** (140 mg, 0.99 mmol) in a mixture 5:3:1 of DCE:H₂O:AcOH (2.24 mL) and the reaction was stirred at 90 ºC. After 5 minutes, 2,5-dimethoxycyclohexanone (0.13 mL, 0.99 mmol) was added and the mixture was stirred at the same temperature overnight. Then, the reaction was cooled to room temperature, diluted with EtOAc and washed with saturated aqueous solution of NaCl. The
organic layer was dried over Na$_2$SO$_4$, filtered and the solvents were concentrated \textit{in vacuo}. The crude product was purified by flash column chromatography (silica gel; petroleum ether/EtOAc, 9:1) to yield 115 mg of 19 (61\% yield) as a white solid. \( R_t = 0.28 \) (petroleum ether/EtOAc, 9:1); mp 55 – 57 °C; \(^1\)H NMR (400 MHz, CDCl$_3$) \( \delta \) 1.94 (s, 3H), 2.05 (t, \( J = 2.6 \) HZ, 1H), 3.00 (dd, \( J = 16.8, 2.6 \) Hz, 1H), 3.07 (dd, \( J = 16.8, 2.6 \) Hz, 1H), 3.74 (s, 3H), 6.21 (t, \( J = 2.2 \) Hz, 2H), 6.83 (t, \( J = 2.2 \) Hz, 2H); \(^{13}\)C NMR (101 MHz, CDCl$_3$) \( \delta \) 22.8, 30.0, 53.1, 63.1, 72.3, 78.5, 108.8, 118.7, 172.0; HRMS (ESI): \( m/z \) calcd for C$_{11}$H$_{14}$NO$_2$ [M+H]$^+$: 192.1019; found: 192.1013.

\textbf{Synthesis of methyl 2-(2-cyano-1H-pyrrol-1-yl)-2-methylpent-4-ynoate (20)}

Chlorosulfonyl isocyanate (0.047 mL, 0.55 mmol) was added drop-wise to a solution of 19 (70 mg, 0.37 mmol) in MeCN (3.6 mL) at 0 °C. After 1 hour stirring, DMF (0.14 mL, 1.85 mmol) was added and the mixture was stirred for 2 hours. Then, saturated aqueous solution of NaHCO$_3$ was added and the reaction mixture was extracted with EtOAc (3x). The combined organic layers were dried over Na$_2$SO$_4$, filtered and the solvents were concentrated \textit{in vacuo}. The crude product was purified by flash column chromatography (silica gel; petroleum ether/EtOAc, 4:1) to yield 57 mg of 20 (71\% yield) as colourless oil. \( R_t = 0.29 \) (petroleum ether/EtOAc; 5:1); mp 64 – 66 °C; \(^1\)H NMR (400 MHz, CDCl$_3$) \( \delta \) 1.88–2.08 (m, 4H), 3.09 (dd, \( J = 17.5, 2.7 \) Hz, 1H), 3.31 (dd, \( J = 17.5, 2.1 \) Hz, 1H), 3.84 (s, 3H), 6.19 (dd, \( J = 3.8, 3.0 \) Hz, 1H), 6.93 (dd, \( J = 3.9, 1.5 \) Hz, 1H), 7.07 (dd, \( J = 2.8, 1.6 \) Hz, 1H); \(^{13}\)C NMR (101 MHz, CDCl$_3$) \( \delta \) 23.8, 29.5, 53.7, 64.5, 72.8, 77.2, 102.9, 108.5, 114.1, 123.2, 125.5, 171.5; HRMS (ESI): \( m/z \) calcd for C$_{12}$H$_{12}$N$_2$NaO$_2$ [M+Na]$^+$: 239.0791; found: 239.0783.
Synthesis of 3,4-dimethyl-3-(prop-2-yn-1-yl)-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione (21)

To a stirred solution of S5 (50 mg, 0.166 mmol) in methanol (1.7 mL) was added zinc (16.3 mg, 0.25 mmol), followed by ammonium formate (32 mg, 0.5 mmol). The resulting mixture was stirred for 2 hours. The reaction mixture was then filtered through a celite pad, washing with CH₂Cl₂. The solvents were removed under reduced pressure and the resulting intermediate was dissolved in DMF (1.7 mL). Sodium hydride (60% in mineral oil, 13 mg, 0.33 mmol) was added to the solution and the mixture was heated at 60 ºC for 2 hours. Then, the mixture was diluted with water and the aqueous layer was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried with Na₂SO₄, filtered, and the solvents were evaporated. The crude product was purified by flash column chromatography (silica gel; petroleum ether/EtOAc, gradient from 1:1 to 0:1) to yield 25 mg of 21 (62% yield) as a white solid. Rₚ = 0.18 (petroleum ether/EtOAc, 1:1); mp 213 – 215 ºC; ¹H NMR (400 MHz, CDCl₃) δ 1.78 (s, 3H), 2.06 (s, 1H), 2.54 (s, 1H), 2.68 (s, 1H), 3.31 (s, 3H), 6.97 (d, J = 8.0 Hz, 1H), 7.20 – 7.27 (m, 1H), 7.46 (td, J = 8.0, 1.5 Hz, 1H), 7.99 (dd, J = 7.9, 1.2 Hz, 1H), 8.79 (br s, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 23.3, 27.7, 32.7, 61.6, 72.8, 119.4, 125.1, 127.6, 131.8, 132.8, 134.6, 168.0, 171.3 (one quaternary carbon coincides with solvent signal); HRMS (EI): m/z calcd for C₁₄H₁₅N₂O₂ [M+H⁺]: 243.1128; found: 243.1133.

Synthesis of methyl 2-(3-ethoxy-3-oxopropanamido)-2-methylpent-4-ynoate (22)
To a solution of 1 (220 mg, 1.56 mmol) in CH₂Cl₂ (15 mL) cooled to 0 ºC, was added ethyl malonyl chloride (0.40 mL, 3.12 mmol) and Et₃N (0.43 mL, 3.12 mmol) and the mixture was stirred for 1 hour. Then, saturated aqueous solution of NH₄Cl was added and the organic layer was separated. The aqueous layer was extracted with CH₂Cl₂ (2x) and the combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silica gel; petroleum ether/EtOAc; 1:1) to afford 379 mg of methyl 2-(3-ethoxy-3-oxopropanamido)-2-methylpent-4-ynoate (S22) (95% yield) as a colourless oil. Rᵣ = 0.34 (petroleum ether/EtOAc, 1:1); ¹H NMR (400 MHz, CDCl₃) δ 1.25 (t, J = 7.1 Hz, 3H), 1.57 (s, 3H), 1.98 (t, J = 2.6 Hz, 1H), 2.93 (d, J = 2.6 Hz, 2H), 3.27 (s, 2H), 3.72 (s, 3H), 4.18 (q, J = 7.1 Hz, 2H), 7.78 (br s, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 14.1, 22.7, 26.4, 41.4, 53.0, 58.7, 61.7, 71.3, 79.2, 164.5, 169.1, 173.1; HRMS (EI): m/z calcd for C₁₂H₁₇NNaO₅ [M+Na]⁺: 278.0999; found: 278.0987.

₉-BuOK (250 mg, 2.22 mmol) was added to a solution of S22 (379 mg, 1.48 mmol) in THF (15 mL) and the resulting mixture was heated at reflux for 2 hours. The mixture warmed to room temperature and then diluted with EtOAc (7 mL) and 1N HCl (7 mL). The aqueous layer was extracted with EtOAc (3x) and the combined organic layers were dried over Na₂SO₄, filtered and the solvents concentrated in vacuo. The resulting residue was dissolved in a mixture MeCN:H₂O (10:1, 15 mL) heated at reflux for 4 hours. The solvents were evaporated in vacuo and the crude product was purified by flash column chromatography (silica gel; petroleum ether/EtOAc, 1:2) to afford 166 mg of 22 (74% yield) as a white solid. Rᵣ = 0.22 (petroleum ether/EtOAc; 1:2); mp 121 – 123 ºC; ¹H NMR (400 MHz, CDCl₃) δ 1.42 (s, 3H), 2.10 (t, J = 2.6 Hz, 1H), 2.54 (qd, J = 16.9, 2.6 Hz, 2H), 3.08 (d,
$J = 2.3$ Hz, 2H), 7.26 (br s, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 23.1, 28.9, 40.6, 67.1, 72.5, 78.0, 170.5, 208.3; HRMS (EI): $m/z$ calcd for C$_8$H$_{10}$NO$_2$ [M+H]$^+$: 152.0706; found: 152.0704.

**Synthesis of tert-butyl 2-((1-(2-ethoxy-2-oxoethyl)-1H,2,3-triazol-5-yl)methyl)-2-methylaziridine-1-carboxylate (23)**

![Synthesis of tert-butyl 2-((1-(2-ethoxy-2-oxoethyl)-1H,2,3-triazol-5-yl)methyl)-2-methylaziridine-1-carboxylate (23)](image)

To a solution of S14 (500 mg, 2.34 mmol) in Et$_2$O (40 mL), was added TsCl (536 mg, 2.81 mmol) and powdered KOH (1052 mg, 18.4 mmol) and the reaction refluxed overnight. The reaction was cooled to room temperature and diluted with water. The aqueous solution was extracted with Et$_2$O (2x) and the combined organic layers dried over Na$_2$SO$_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica gel; petroleum ether/EtOAc, 4:1) to give 357 mg of 23 (78%) as a colourless oil. $R_f = 0.55$ (petroleum ether/EtOAc 9:1); $^1$H NMR (400 MHz, CDCl$_3$) δ 1.39 (s, 3H), 1.48 (s, 9H), 2.08 (t, $J = 2.7$ Hz, 1H), 2.12 (s, 1H), 2.25 (s, 1H), 2.37 (dd, $J = 17.1, 2.7$ Hz, 1H), 2.56 (dd, $J = 17.1, 2.6$ Hz, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 19.7, 27.1, 28.0, 36.4, 41.1, 71.0, 79.6, 81.1, 160.6; HRMS (EI): $m/z$ calcd for C$_{11}$H$_{18}$NO$_2$ [M+H]$^+$: 196.1332, found 196.1333.

**Synthesis of 5-methyl-5-(prop-2-yn-1-yl)morpholin-2-one (24)**

![Synthesis of 5-methyl-5-(prop-2-yn-1-yl)morpholin-2-one (24)](image)
To a solution of S14 (84.0 mg, 0.394 mmol) and trimethylamine (65 uL, 0.473 mmol) in CH₂Cl₂ (3 mL) at 0 °C was added chloroacetyl chloride (37.6 uL, 0.473 mmol) and the reaction warmed to room temperature before heating to 40 °C for 7 hours. Further chloroacetyl chloride (9.40 uL, 0.118 mmol) was added and the reaction heated for a further 1.5 hours. Then, the reaction was cooled to room temperature, diluted with H₂O and extracted with CH₂Cl₂ (3x). The combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silica gel; petroleum ether/EtOAc 3:2) to give 80 mg of 2-((tert-butoxycarbonyl)amino)-2-methylpent-4-yn-1-yl 2-chloroacetate (S23) (70%) as a colourless oil. Rᵣ = 0.14 (petroleum ether/EtOAc, 17:3); ¹H NMR (400 MHz, CDCl₃) δ 1.40 (s, 3H), 1.44 (s, 9H), 2.06 (t, J = 2.6 Hz, 1H), 2.57 (dd, J = 16.8, 2.6 Hz, 1H), 2.72 – 2.81 (m, 1H), 4.10 (s, 2H), 4.35 (d, J = 11.0 Hz, 1H), 4.43 (d, J = 11.0 Hz, 1H), 4.70 (s, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 21.9, 26.8, 28.3, 40.7, 53.9, 68.6, 71.6, 79.3, 79.9, 154.3, 166.9; HRMS (EI): m/z calcd for C₁₃H₂₁NO₄Cl [M+H]⁺: 290.1159, found 290.1144.

To a solution of S23 (24.0 mg, 0.0830 mmol) in CH₂Cl₂ (0.9 mL) was added TFA (0.85 mL) and the reaction stirred for 2.5 hours. The reaction was concentrated in vacuo to afford the intermediate as a colourless gum. To a solution of this intermediate (40 mg, 0.138 mmol) in THF (1.3 mL) was added triethylamine (77 uL, 0.553 mmol) and the reaction stirred for 6 hours. The, the reaction was diluted with water and extracted with CH₂Cl₂ (3x). The combined organic layers were washed with NH₄Cl, dried over Na₂SO₄, filtered and concentrated in vacuo to give 24 (16 mg, 0.105 mmol, 76%) as a colourless oil. Rᵣ = 0.41 (petroleum ether/EtOAc, 1:1); ¹H NMR (400 MHz, CDCl₃) δ 1.42 (s, 3H), 2.13 (t, J = 2.6 Hz, 1H), 2.51 (dd, J = 16.9, 2.6 Hz, 1H), 2.81 (dd, J = 16.9, 2.6 Hz, 1H), 3.75 (s, 2H), 4.05 (s, 2H), 6.93 (s, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 22.1, 26.7, 42.8, 57.8, 68.2, 71.9, 79.3, 166.6; HRMS (EI): m/z calcd for C₉H₁₂NO₂ [M+H]⁺: 154.0863, found 154.0862.

**Synthesis of 5-methyl-5-(prop-2-yn-1-yl)morpholin-3-one (24)**
To a solution of **S14** (140 mg, 0.656 mmol) in CH₂Cl₂ (1 mL) was added HCl (2M in Et₂O) (4.28 mL, 0.856 mmol) and the reaction stirred for 22 hours. Then, the reaction was concentrated *in vacuo* to give the intermediate salt. A solution of the intermediate (93 mg) in CH₂Cl₂ (6.5 mL) was cooled to 0 °C before triethylamine (0.260 mL, 1.968 mmol) was added. Chloroacetyl chloride (59 uL, 0.744 mmol) was added drop-wise and the reaction was warmed to room temperature and stirred for 5 hours. Then, a saturated aqueous solution of NH₄Cl (30 mL) was added and extracted with EtOAc (3x). The combined organics were dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica gel; petroleum ether/EtOAc 7:3) to give 102 mg of 2-chloro-N-(1-hydroxy-2-methylpent-4-yn-2-yl)acetamide (**S24**) (88%) as a colourless oil. \( R_f = 0.21 \) (petroleum ether/EtOAc 3:2); \(^1\text{H NMR} (400 \text{ MHz, CDCl}_3) 1.39 (s, 3H), 2.10 (t, \text{ J} = 2.7 \text{ Hz}, 1\text{H}), 2.47 (dd, \text{ J} = 16.9, 2.6 \text{ Hz}, 1\text{H}), 2.78 (dd, \text{ J} = 16.9, 2.7 \text{ Hz}, 1\text{H}), 3.72 (s, 2\text{H}), 3.94 (s, 1\text{H}), 4.03 (s, 2\text{H}), 6.90 (br s, 1\text{H}); \(^{13}\text{C NMR} (101 \text{ MHz, CDCl}_3) \delta 22.1, 26.8, 42.8, 57.8, 68.2, 72.0, 79.3, 166.6; \) HRMS (El): \text{m/z} \text{ calcd for C}_{8}\text{H}_{13}\text{NO}_{2}\text{Cl} [\text{M+H}]^+: 190.0629, \text{found } 190.0629.

To a solution of **S24** (102 mg, 0.540 mmol) in t-BuOH (5.4 mL) was added t-BuOK (65 mg, 0.579 mmol) and the reaction heated to 30 °C for 6 hours. Then, NH₄Cl (sat. aq.) was added and the solution extracted with EtOAc (3x). The combined organics were dried over MgSO₄ and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica gel; petroleum ether/EtOAc 7:3) to give 60 mg of **25** (73%) as a white solid. \( R_f = 0.09 \) (petroleum ether/EtOAc 3:2); \text{mp} 77 – 79°C; \(^1\text{H NMR} (400 \text{ MHz, CDCl}_3) \delta 1.36 (s, 3\text{H}), 2.13 (t, \text{ J} = 2.6 \text{ Hz}, 1\text{H}), 2.46 (dd, \text{ J} = 16.5, 2.6 \text{ Hz}, 1\text{H}), 2.59 (dd, \text{ J} = 16.5, 2.6 \text{ Hz}, 1\text{H}), 3.55 (d, J
= 11.8 Hz, 1H), 3.77 (d, J = 11.8 Hz, 1H), 4.10 – 4.23 (m, 2H), 6.34 (s, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 23.5, 29.8, 53.7, 67.6, 71.8, 72.1, 78.8, 125.0, 168.2; HRMS (El): m/z calcd for C$_8$H$_{12}$NO$_2$ [M+H]$^+$: 154.0863, found 154.0863.

**Synthesis of 4-methyl-4-(prop-2-yn-1-yl)oxazolidin-2-one (26)**

To a of S14 (33 mg, 0.155 mmol) in THF (1.60 mL) at 0 ºC was added t-BuOK (35 mg, 0.31 mmol) and the reaction warmed room temperature and stirred for 6 hours. Then, the reaction was diluted with NH$_4$Cl saturated aqueous solution and extracted with CH$_2$Cl$_2$ (3x). The combined organic extracts were dried over Na$_2$SO$_4$, filtered and concentrated in vacuo to give 14.7 mg of 26 (67 %) as a white solid without further purification. $R_f = 0.26$ (petroleum ether/EtOAc, 1:1); m 83 – 85 ºC; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.48 (s, 3H), 2.12 (t, J = 2.6 Hz, 1H), 2.45 – 2.56 (m, 2H), 4.12 (d, J = 8.7 Hz, 1H), 4.30 (d, J = 8.7 Hz, 1H), 5.95 (s, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$); 25.0, 30.9, 57.1, 71.8, 74.9, 78.5, 158.5; HRMS (El): m/z calcd for C$_7$H$_{10}$NO$_2$ [M+H]$^+$: 140.0706, found 140.0708.

**Synthesis of 3-methyl-5-methylene-3-(1H-pyrrol-1-yl)dihydrofuran-2(3H)-one (27)**

NaOAc (26 mg, 0.32 mmol) was added to a stirred solution of 19 (30 mg, 0.16 mmol) in a mixture 5:3: of DCE:H$_2$O:AcOH (1.6 mL) and the reaction was stirred at 90 ºC for 24 hours. Then, the reaction was cooled to room temperature, diluted with EtOAc and washed with
saturated aqueous solution of NaCl. The organic layer was dried over Na₂SO₄, filtered and the solvents were concentrated in vacuo. The crude product was purified by flash column chromatography to yield 12 mg of 27 (42% yield) as a colourless oil. \( R_f = 0.22 \) (petroleum ether/EtOAc, 9:1); \(^1\)H NMR (400 MHz, CDCl₃) \( \delta \)1.85 (s, 3H), 3.11 (dt, \( J = 16.2, 1.5 \) Hz, 1H), 3.39 (dt, \( J = 16.2, 1.8 \) Hz, 1H), 4.51 (dt, \( J = 3.2, 1.7 \) Hz, 1H), 4.91 (dt, \( J = 2.8, 2.1 \) Hz, 1H), 6.24 (t, \( J = 2.2 \) Hz, 2H), 6.86 (t, \( J = 2.1 \) Hz, 2H); \(^{13}\)C NMR (101 MHz, CDCl₃) \( \delta \) 24.2, 41.5, 61.6, 91.2, 109.7, 118.4, 151.3, 173.5; HRMS (ESI): \( m/z \) calcd for C₁₀H₁₂NO₂ [M+H]⁺: 178.0861; found: 178.0863.

**Synthesis of methyl 5-methyl-5,6-dihydroindolizine-5-carboxylate (28)**

\[
\begin{align*}
\text{Me} & \quad \text{Me} \\
\text{N} & \quad \text{CO}_2\text{Me} \\
\text{AuSPhos(MeCN)SbF}_6 & \quad \text{DCE:EtOH, 40 °C, 2 h} \\
19 & \quad 28
\end{align*}
\]

A solution of AuSPhos(MeCN)SbF₆ (4.8 mg, 5 mol%) in DCE (0.1 mL) was added drop-wise to a solution of 19 (21 mg, 0.11 mmol) and ethanol (0.032 mL, 0.55 mmol) in DCE (1.0 mL). The resulting solution was heated for 2 hours at 40 °C and then the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (silica gel; petroleum ether /EtOAc, 4:1) to yield 17 mg of 28 (81% yield) as a colourless oil. \( R_f = 0.24 \) (petroleum ether/EtOAc, 5:1); \(^1\)H NMR (400 MHz, CDCl₃) \( \delta \) 1.80 (s, 3H), 2.49 (dt, \( J = 16.9, 2.7 \) Hz, 1H), 2.95 (dd, \( J = 16.9, 6.1 \) Hz, 1H), 3.64 (s, 3H), 5.58 – 5.69 (m, 1H), 6.12 (d, \( J = 2.5 \) Hz, 1H), 6.22 (t, \( J = 3.2 \) Hz, 1H), 6.46 (dd, \( J = 9.7, 2.8 \) Hz, 1H), 6.85 (s, 1H); \(^{13}\)C NMR (101 MHz, CDCl₃) \( \delta \) 24.0, 35.8, 52.9, 61.3, 107.4, 108.9, 117.1, 118.9, 120.8, 130.3, 174.0; HRMS (ESI): \( m/z \) calcd for C₁₁H₁₄NO₂ [M+H]⁺: 192.1019; found: 192.1012.
Synthesis of methyl 2-cyclopropyl-6-methyl-5,6-dihydropyrrolo[1,2-\(h\)][1,7]naphthyridine-6-carboxylate (29) and methyl 3-cyclopropyl-6-methyl-5,6-dihydropyrrolo[1,2-\(h\)][1,7]naphthyridine-6-carboxylate (30)

CpCo(CO)\(_2\) (13.3 mg, 0.038 mmol) and cyclopropylacetylene (0.048 mL, 0.57 mmol) were added to a solution of 20 (40 mg, 0.19 mmol) in toluene (3.5 mL), previously degassed with argon for 15 minutes, and the mixture was heated at 110 °C for 36 hours. Then, the solvent was removed under reduced pressure and the crude product was purified by column chromatography (silica gel; gradient from petroleum/EtOAc, gradient from 4:1 to 2:1) to afford 14 mg of 29 (27% yield) and 5 mg of 30 (10% yield) both as a white solids.

**Data of major regioisomer (29):**

\(R_f = 0.34\) (petroleum ether/EtOAc; 4:1); mp 108 – 110 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 0.94\) (dd, \(J = 8.2, 3.3\) Hz, 2H), 0.99 – 1.12 (m, 2H), 1.88 (s, 3H), 1.95 – 2.07 (m, 1H), 3.06 (d, \(J = 15.4\) Hz, 1H), 3.43 (d, \(J = 15.5\) Hz, 1H), 3.54 (s, 3H), 6.33 (t, \(J = 3.2\) Hz, 1H), 6.79 (d, \(J = 7.8\) Hz, 1H), 6.90 – 6.99 (m, 2H), 7.28 (d, \(J = 7.8\) Hz, 1H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta 9.7, 17.2, 24.3, 39.4, 53.0, 61.2, 107.9, 110.1, 117.8, 120.0, 120.2, 131.5, 135.1, 146.9, 161.7, 173.1; HRMS (ESI): \(m/z\) calcd for C\(_{17}\)H\(_{19}\)N\(_2\)O\(_2\) [M+H]+: 283.1441; found: 283.1435.

**Data of minor regioisomer (30):**

\(R_f = 0.23\) (petroleum ether/EtOAc; 2:1); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 0.67 – 0.75\) (m, 2H), 0.97 – 1.03 (m, 2H), 1.82 – 1.92 (m, 4H), 3.08 (d, \(J = 15.5\) Hz, 1H), 3.43 (d, \(J = 15.5\) Hz, 1H), 3.54 (s, 3H), 6.35 (t, \(J = 3.0\) Hz, 1H), 6.94 (s, 2H), 7.07 (s, 1H), 8.25 (s, 1H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta 8.9, 9.0, 13.1, 24.3, 39.8, 53.1, 61.0, 107.6, 110.3, 120.0, 123.5, 131.0,\)
Synthesis of 4-methyl-4-propyl-1,2-dihydropyrrolo[1,2-a]pyrazin-3(4H)-one (31)

PtO₂ (34 mg, 0.15 mmol) was added to a solution of 20 (35 mg, 0.15 mmol) in MeOH (3 mL) and the reaction mixture was stirred under H₂ atmosphere (1 atm) for 16 h. Then, the resulting suspension was filtered and the filtrate was concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel; petroleum ether/EtOAc, 1:1) to yield 10 mg of 31 (35% yield) as colourless oil. Rf = 0.24 (petroleum ether/EtOAc; 1:1); ¹H NMR (400 MHz, CDCl₃) δ 0.82 (t, J = 7.2 Hz, 3H), 0.88 – 1.01 (m, 1H), 1.11 – 1.23 (m, 1H), 1.27 (d, J = 4.5 Hz, 3H), 1.82 (ddd, J = 13.6, 10.3, 4.3 Hz, 1H), 2.16 (ddd, J = 13.7, 12.1, 4.6 Hz, 1H), 4.52 – 4.63 (m, 2H), 5.93 (d, J = 2.0 Hz, 1H), 6.25 (t, J = 3.2 Hz, 1H), 6.35 (s, 1H), 6.69 (dd, J = 2.4, 1.8 Hz, 1H); ¹³C NMR (126 MHz, CDCl₃) δ 14.0, 17.4, 26.4, 39.8, 43.7, 62.9, 102.8, 109.8, 115.9, 122.1, 172.2; HRMS (ESI): m/z calcd for C₁₇H₁₉N₂O [M+H]+: 283.1441; found: 283.1440.

Synthesis of 8a-methyl-6,8a-dihydro-1H-pyrrolo[2,1-c][1,4]oxazin-4(3H)-one (32)

InCl₃ (188 mg, 0.852 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 (4
mL) was added under Argon. The mixture was stirred at room temperature for 10 min and then cooled to −78 ºC. DIBAL-H (1.0 M in hexane, 0.852 mL, 0.852 mmol) was added dropwise and the mixture was stirred at −78 ºC for 40 min. Then, 25 (87 mg, 0.570 mmol) in THF (1 mL) was then added, followed by Et₃B (1.0 M in THF, 0.284 mL, 0.284 mmol) and the mixture was stirred at −78 ºC for 4.5 hours. A solution of iodine (865 mg, 3.41 mmol) in THF (1 mL) was then added. After 1 hour, the mixture was poured onto a saturated solution of NaHCO₃ (5 mL). Na₂S₂O₃ was added under stirring until complete decoloration and the aqueous layer was extracted with EtOAc (5x). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated in vacuo. The crude sample was purified over a short column (silica gel; petroleum ether/EtOAc, 7:3). The crude product (90 mg), Cs₂CO₃ (121 mg, 0.373 mmol) Cul (24 mg, 0.124 mmol) and N,N-dimethylethyl-1,2-diamine (27 uL, 0.249 mmol) in toluene (2 mL) were heated to 80 ºC for 3 hours (in a sealed tube). H₂O (10 mL) was added and the reaction extracted with CH₂Cl₂ (5x). The combined organic extracts were washed with brine (10 mL), dried over Na₂SO₄, filtered and concentrated in vacuo to give a mixture of desired product and unreacted 25 (ca. 50:50 determined by ¹H NMR). The crude product was purified by flash column chromatography (silica gel; petroleum ether/EtOAc, 7:3) to give 12 mg of 32 (24%) as a white solid (based on 43% recovered unreacted starting material). Rₜ = 0.17 (petroleum ether/EtOAc, 7:3); mp 77 – 79 ºC; ¹H NMR (400 MHz, CDCl₃) δ 1.40 (s, 3H), 2.34 (ddd, J = 15.8, 3.1, 1.3 Hz, 1H), 2.58 (dt, J = 15.8, 2.5 Hz, 1H), 3.57 (d, J = 11.2 Hz, 1H), 3.92 (d, J = 11.2 Hz, 1H), 4.08 (d, J = 17.1 Hz, 1H), 4.28 (d, J = 17.1 Hz, 1H), 5.33 (ddd, J = 4.4, 3.1, 2.2 Hz, 1H), 6.83 – 6.88 (m, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 23.9, 40.4, 61.4, 66.0, 72.2, 111.2, 127.2, 163.8; HRMS (ESI): m/z calcd for C₈H₁₂N₂O [M+H]⁺: 154.0868, found 154.0870.

Synthesis of 7a-methyl-5,7a-dihydro-1H,3H-pyrrolo[1,2-c]oxazol-3-one (33)
InCl₃ (62 mg, 0.28 mmol) was introduced into 5 mL flask and heated with a heat gun (150 °C) under vacuum for 2 min. After being allowed to cool to room temperature, THF (0.8 mL) was added under Argon. The mixture was stirred at room temperature for 10 min and cooled to −78 °C. DIBAL-H (1.0 M in hexane, 0.27 mL, 0.27 mmol) was added drop-wise and the mixture was stirred at −78 °C for 40 min. Then, 26 (25 mg, 0.18 mmol) was then added, followed by Et₃B (1.0 M in THF, 0.09 mL, 0.09 mmol) and the mixture was stirred at −78 °C for 3 hours. A solution of iodine (274 mg, 1.08 mmol) in THF (0.4 mL) was then added. After 40 min, the mixture was poured onto a saturated solution of NaHCO₃ (5 mL). Na₂S₂O₃ was added under stirring until complete decoloration and the aqueous layer was extracted with EtOAc (5x). The combined organic layers were dried over Na₂SO₄, filtered and concentrated \textit{in vacuo}. The crude product was dissolved in toluene (1.8 mL) and CuI (15 mg, 0.08 mmol), Cs₂CO₃ (70 mg, 0.22 mmol) and \textit{N,N’}-dimethylethane-1,2-diamine (17 μL, 0.16 mmol) were added. The mixture was stirred at 85 °C for 2 hours (in a sealed tube). Then, the reaction was cooled to room temperature, diluted with CH₂Cl₂ (5 mL) and washed with water (5 mL). The aqueous layer was extracted with CH₂Cl₂ (3x) and the combined organic layers were dried over Na₂SO₄, filtered and concentrated \textit{in vacuo}. The crude product was purified by flash column chromatography (silica gel; EtOAc/petroleum ether 2:1) to give 7 mg of 33 (28%) as a colourless oil. \( R_f = 0.14 \) (petroleum ether/EtOAc, 17:3); \(^1\)H NMR (400 MHz, CDCl₃) 1.39 (s, 3H), 2.37 (qd, \( J = 11.5, 2.8 \) Hz, 1H), 2.71 (dt, \( J = 16.6, 2.6 \) Hz, 1H), 4.20 (d, \( J = 8.6 \) Hz, 1H), 4.28 (d, \( J = 8.6 \) Hz, 1H), 5.23 – 5.21 (m, 1H), 6.38 – 6.35 (m, 1H); \(^{13}\)C NMR (101 MHz, CDCl₃) 26.7, 42.8, 64.9, 77.3, 112.6, 127.1, 157.1; HRMS (ESI) \( m/z \) calcd for [C₇H₁₀NO₂]⁺: 140.0706, found 140.0712.
Synthesis of methyl 2-methyl-3-(1-phenyl-1H,2,3-triazol-4-yl)-2-(1H-pyrrol-1-yl)propanoate (19a)

CuSO₄·5H₂O (1.2 mg, 0.041 mmol) and sodium ascorbate (6.2 mg, 0.03 mmol) were added to a stirred solution of 19 (20 mg, 0.105 mmol) and azidobenzene (0.5 M in tert-butyl methyl ether, 0.3 mL, 0.156 mmol) in a mixture 1:1 of t-BuOH:H₂O (0.5 mL). The mixture was stirred at room temperature overnight. The reaction mixture was concentrated in vacuo and the aqueous layer was extracted with EtOAc (3x). The combined organic layer was washed with 5% aqueous solution of NH₄OH, dried over Na₂SO₄, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silica gel; petroleum ether/EtOAc, 2:1) to yield 30 mg of 19a (92% yield) as white solid. Rf = 0.34 (petroleum ether/EtOAc, 2:1); mp 100 – 102 ºC; ¹H NMR (400 MHz, CDCl₃) δ 1.73 (s, 3H), 3.61 (s, 2H), 3.79 (s, 3H), 6.23 (t, J = 2.2 Hz, 2H), 6.60 (s, 1H), 6.78 (t, J = 2.2 Hz, 2H), 7.34 – 7.43 (m, 1H), 7.43 – 7.49 (m, 2H), 7.52 – 7.59 (m, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 21.8, 36.3, 53.2, 63.8, 108.9, 119.1, 120.4, 120.8, 128.6, 129.8, 137.1, 142.3, 173.0; HRMS (ESI): m/z calcd for C₁₇H₁₈N₄NaO₂ [M+Na]⁺: 333.1327; found: 333.1331.

Synthesis of 3,4-dimethyl-3-((1-phenyl-1H,2,3-triazol-4-yl)methyl)-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione (21a)
CuSO$_4$·5H$_2$O (3.4 mg, 0.0135 mmol, 8 mol%) and sodium ascorbate (16 mg, 0.08 mmol) were added to a solution of 21 (41 mg, 0.17 mmol) and azidobenzene (0.5 M in tert-butyl methyl ether, 0.54 mL, 0.27 mmol) in a mixture 1:1 of t-BuOH:H$_2$O (0.2 mL). The mixture was stirred at room temperature for 24 hours and then the solvents were removed in vacuo. The residue was diluted with brine and then extracted with CH$_2$Cl$_2$ (3x). The combined organic layers were washed with 5% aqueous solution of NH$_4$OH, dried over Na$_2$SO$_4$, filtered and solvent was removed in vacuo. The crude product was purified by flash column chromatography (silica gel; petroleum ether/EtOAc, gradient from 1:2 to 0:1) to afford 47 mg of 21a (77% yield) as a white solid. $R_f = 0.22$ (petroleum ether/EtOAc, 1:2); mp 190 – 192°C; $^1$H NMR (400 MHz, CDCl$_3$) δ 1.79 (br s, 3H), 3.12 (br s, 1H), 3.16 (s, 3H), 3.20 (d, $J = 14.7$ Hz, 1H), 7.02 (d, $J = 7.9$ Hz, 1H), 7.23 – 7.31 (m, 2H), 7.41 – 7.46 (m, 1H), 7.47 – 7.53 (m, 3H), 7.61 (s, 1H), 7.64 – 7.69 (m, 2H), 8.10 (dd, $J = 7.9$, 1.2 Hz, 1H), 8.55 (s, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 23.3, 32.5, 32.8, 62.6, 62.6, 119.6, 120.6, 120.7, 125.1, 127.6, 129.0, 129.9, 131.8, 133.1, 135.1, 137.0, 142.3, 168.2, 171.9; HRMS (ESI): $m/z$ calcd for C$_{20}$H$_{20}$N$_5$O$_2$ [M+H]$^+$: 362.1612; found: 362.1611.

**Synthesis of 5-methyl-5-((1-phenyl-1H-1,2,3-triazol-4-yl)methyl)pyrrolidine-2,4-dione (22a)**
CuSO₄·5H₂O (6.7 mg, 0.027 mmol) and sodium ascorbate (16 mg, 0.08 mmol) were added to a solution of 22 (41 mg, 0.27 mmol) and azidobenzene (0.5 M in tert-butyl methyl ether, 0.54 mL, 0.27 mmol) in a mixture 1:1 of t-BuOH:H₂O (0.2 mL). The mixture was stirred for 24 hours and then solvents were removed in vacuo. The residue was dissolved in brine and then extracted with CH₂Cl₂ (3x). The combined organic layers were washed with 5% aqueous solution of NH₄OH, dried over Na₂SO₄, filtered and solvent was removed in vacuo. The crude product was purified by flash column chromatography (silica gel; EtOAc/MeOH, gradient from 0:1 to 25:1) to afford 56 mg of 22a (77% yield) as a white solid. *R*ᵣ = 0.31 (EtOAc/MeOH, 25:1); mp 188 – 190 °C; ¹H NMR (400 MHz, CDCl₃) δ 1.46 (s, 3H), 2.87 (d, *J* = 22.2 Hz, 1H), 3.04 (d, *J* = 22.2 Hz, 1H), 3.13 (d, *J* = 14.9 Hz, 1H), 3.22 (d, *J* = 14.9 Hz, 1H), 7.41 (t, *J* = 7.3 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 2H), 7.66 (d, *J* = 7.8 Hz, 2H), 7.77 (br s, 1H), 7.86 (s, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 23.9, 33.9, 40.4, 67.9, 120.4, 121.0, 129.0, 129.9, 136.9, 142.5, 170.1, 209.8; HRMS (El): *m/z* calcd for C₁₄H₁₅N₄O₂ [M+H]⁺: 271.1195; found: 271.1192.

Synthesis of 4-methyl-4-((1-phenyl-1H-1,2,3-triazol-4-yl)methyl)oxazolidin-2-one (26a)
CuSO₄·5H₂O (6.7 mg, 0.027 mmol) and sodium ascorbate (16 mg, 0.08 mmol) were added to a solution of 26 (20.0 mg, 0.140 mmol) and azidobenzene (0.5 M in tert-butyl methyl ether, 0.431 mL, 0.215 mmol) in a mixture 1:1 of t-BuOH:H₂O (1 mL). The mixture was stirred for 24 hours and then solvents were removed in vacuo. The residue was dissolved in brine and then extracted with CH₂Cl₂ (3x). The combined organic layers were washed with 5% aqueous solution of NH₄OH, dried over Na₂SO₄, filtered and solvent was removed in vacuo. The crude product was purified by flash column chromatography (100% EtOAc) to give 26 mg of 26a (72%) as a white solid. \( R_f = 0.12 \) (petroleum ether/EtOAc 1:1); mp 147.3 – 146.7 °C; \(^1\)H NMR (400 MHz, CDCl₃) 1.41 (s, 3H), 3.10 – 3.02 (m, 2H), 4.11 (d, J = 8.6 Hz, 1H), 6.97 (s, 1H), 4.40 (d, J = 8.6 Hz, 1H), 7.40 – 7.36 (m, 1H), 7.48 – 7.43 (m, 2H), 7.71 – 7.67 (m, 2H), 7.99 (s, 1H); \(^1\)C NMR (101 MHz, CDCl₃) 26.0, 36.3, 57.7, 75.1, 120.4, 121.1, 128.7, 129.7, 136.9, 142.9, 159.3; HRMS (ESI) \( m/z \) calcd for \([\text{C}_{13}\text{H}_{15}\text{N}_{4}\text{O}_2]^+\): 259.1190, found 259.1196.

**Synthesis of 3,4-dimethyl-3-(3-phenylprop-2-yn-1-yl)-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione (21b)**
A solution of 21 (25 mg, 0.1 mmol) in DMF (1.2 mL) was added over a period of 1 hour to a mixture of PdCl$_2$(PPh$_3$)$_2$ (3.5 mg, 5 mmol%), Cul (1.9 mg, 10 mmol%), Et$_3$N (0.15 mL), and benzyl 2-iodobenzoate (0.016 mL, 0.15 mmol) in degassed DMF (2.5 mL). After 16 hours, the reaction mixture was diluted with EtOAc and washed with saturated aqueous solution of NaHCO$_3$ and brine. The organic layer was dried over Na$_2$SO$_4$, filtered and the solvents were removed in vacuo. The crude product was purified by flash column chromatography (silica gel; petroleum ether/EtOAc, 2:1) to yield 19 mg of 21b (60% yield) as a white solid. $R_f = 0.34$ (petroleum ether/EtOAc, 2:1); mp 225 – 227 °C; $^1$H NMR (400 MHz, CDCl$_3$) δ 1.86 (br s, 3H), 2.75 (br s, 1H), 2.90 (br s, 1H), 3.38 (s, 3H), 6.99 (d, $J = 8.0$ Hz, 1H), 7.21 – 7.34 (m, 4H), 7.34 – 7.43 (m, 2H), 7.48 (t, $J = 7.5$ Hz, 1H), 8.04 (d, $J = 7.8$ Hz, 1H), 8.67 (s, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 23.7, 28.8, 32.7, 62.0, 83.4, 84.7, 119.4, 122.9, 125.1, 127.6, 128.4, 128.4, 131.7, 131.9, 132.8, 134.7, 168.1, 171.6; HRMS (ESI): m/z calcd for C$_{20}$H$_{18}$N$_2$NaO$_2$ [M+Na]$^+$: 341.1260; found: 341.1253.

**Synthesis of 5-methyl-5-(3-phenylprop-2-yn-1-yl)pyrrolidine-2,4-dione (22b)**

A solution of 22 (25 mg, 0.165 mmol) in DMF (1.2 mL) was added over a period of 1 hour to a mixture of PdCl$_2$(PPh$_3$)$_2$ (3.5 mg, 0.005 mmol), Cul (1.9 mg, 0.01 mmol), Et$_3$N (0.15 mL), and benzyl 2-iodobenzoate (0.016 mL, 0.15 mmol) in degassed DMF (2.5 mL). After 16 hours, the reaction mixture was diluted with EtOAc and washed with saturated aqueous solution of NaHCO$_3$ and brine. The organic layer was dried over Na$_2$SO$_4$, filtered and the solvents were removed in vacuo. The crude product was purified by flash column chromatography (silica gel; petroleum ether/EtOAc, 2:1) to yield 10 mg of 22b (26% yield) as
a white solid. $R_f = 0.29$ (petroleum ether/EtOAc, 2:1); mp 93 – 95 ºC; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.48 (s, 3H), 2.73 (d, $J = 16.9$ Hz, 1H), 2.82 (d, $J = 16.9$ Hz, 1H), 3.02 – 3.19 (m, 2H), 7.24 (s, 1H), 7.26 – 7.35 (m, 3H), 7.35 – 7.43 (m, 2H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 23.1, 30.0, 40.6, 67.4, 83.2, 84.5, 122.5, 128.5, 128.6, 131.8, 170.4, 208.5; HRMS (EI): m/z calcd for C$_{14}$H$_{14}$NO$_2$ [M+H]$^+$: 228.1025; found: 228.1019.

**Synthesis of 3,4-dimethyl-3-propyl-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione (21c)**

Pd/C (10% wt, 4.4 mg, 10 mol %) was added to a solution of 21 (10 mg, 0.041 mmol) in MeOH (1 mL) and the mixture was stirred under H$_2$ atmosphere (1 atm) for 2 hours. Then, the mixture was filtered through celite and the filtrate was concentrated in vacuo. The crude product was purified by flash column chromatography (silica gel; EtOAc/MeOH, 20:1) to yield 7 mg of 21c (69% yield) as a white solid. $R_f = 0.30$ (EtOAc/MeOH, 20:1); mp 156 – 158 ºC; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 0.64 (t, $J = 7.2$ Hz, 3H). 1.17 – 1.28 (m, 2H), 1.39 – 1.49 (m, 1H), 1.55 – 1.63 (m, 1H), 1.68 (s, 3H), 3.24 (s, 3H), 6.91 (d, $J = 8.0$ Hz, 1H), 7.21 (t, $J = 7.6$ Hz, 1H), 7.44 (t, $J = 7.6$ Hz, 1H), 7.96 (d, $J = 7.9$ Hz, 1H), 8.38 (s, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 14.1, 17.4, 23.1, 32.6, 38.4, 62.9, 119.1, 124.8, 127.8, 131.4, 132.5, 134.9, 168.3, 173.3; HRMS (EI): m/z calcd for C$_{14}$H$_{18}$KN$_2$O$_2$ [M+K]$^+$: 285.1005; found: 285.0989.

**Synthesis of 5-methyl-5-propylpyrrolidine-2,4-dione (22c)**
Pd/C (10% wt, 15.5 mg, 10 mol %) was added to a solution of 22 (22 mg, 0.15 mmol) in MeOH (3 mL) and the mixture was stirred under H$_2$ atmosphere (1 atm) for 2 hours. Then, the mixture was filtered through celite and the filtrate was concentrated in vacuo. The crude product was purified by flash column chromatography (silica gel; petroleum ether/EtOAc, 2:1) to afford 20 mg of 22c (87% yield) as a white solid. $R_f = 0.29$ (petroleum ether/EtOAc, 1:2); mp 94 – 96 ºC; $^1$H NMR (400 MHz, CDCl$_3$) δ 0.91 (t, $J = 7.3$ Hz, 3H), 1.12 – 1.22 (m, 1H), 1.34 (s, 3H), 1.39 – 1.51 (m, 1H), 1.56 (ddd, $J = 13.9, 12.4, 4.4$ Hz, 1H), 1.73 (ddd, $J = 13.9, 12.2, 4.8$ Hz, 1H), 2.97 (d, $J = 22.2$ Hz, 1H), 3.04 (d, $J = 22.2$ Hz, 1H), 7.17 (br s, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 14.2, 17.3, 24.0, 40.6, 40.7, 68.6, 170.6, 210.3; HRMS (EI): m/z calcd for C$_8$H$_{13}$NNaO$_2$ [M+Na]$^+$: 178.0844; found: 178.0845.

Synthesis of tert-butyl 2-((1-(2-ethoxy-2-oxoethyl)-1H,1,2,3-triazol-5-yl)methyl)-2-methylaziridine-1-carboxylate (23d)

A solution of 23 (50.0 mg, 0.256 mmol) and ethyl 2-azidoacetate (49.6 mg, 0.384 mmol) in toluene (3 mL) was degassed with an argon purge. Cp*Ru(COD)Cl (3.90 mg, 0.0102 mmol) was added at room temperature for 18 hours and then heated to 60 ºC for 3 hours. Further Cp*Ru(COD)Cl (7.80 mg, 0.0204 mmol) was added and the reaction stirred at the same temperature for 24 hours. Then, the reaction was concentrated in vacuo and the crude product purified by flash column chromatography (silica gel; petroleum ether/EtOAc, gradient from 1:1 to 0:1) to yield 35 mg of 23d (42%) as a brown oil. $R_f = 0.12$ (petroleum ether/EtOAc, 1:1); $^1$H NMR (400 MHz, CDCl$_3$) δ 1.27 (s, 3H), 1.30 (t, $J = 7.1$ Hz, 3H), 1.44 (s, 9H), 2.03 (s, 1H), 2.19 (s, 1H), 2.75 (d, $J = 15.5$ Hz, 1H), 3.03 (d, $J = 15.5$ Hz, 1H), 4.25 (qd, $J = 7.1, 1.5$ Hz, 2H), 5.28 (d, $J = 17.8$ Hz, 1H), 5.43 (d, $J = 17.8$ Hz, 1H), 7.63 (s, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 14.1, 19.0, 28.0, 31.1, 35.9, 41.3, 49.4, 62.1, 81.7, 133.6,
SYNTHESIS OF THE PHENYL-CONTAINING DERIVATIVE 10’

Synthesis of methyl 2-amino-2-phenylpent-4-ynoate (1’)

Propargyl bromide (80 wt. % in toluene, 1.16 mL, 12.25 mmol) and activated zinc powder (801 mg, 12.25 mmol) were added to a stirred solution of methyl 2-((4-methoxyphenyl)imino)-2-phenylacetate (2.2 g, 8.16 mmol) in DMF (40 mL) cooled at 0 °C. The reaction mixture was then slowly warmed to room temperature and heated at 60 °C for 1 hour. Then, the mixture was cooled to 0 °C, quenched with saturated aqueous solution of NH₄Cl and the aqueous layer was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried with Na₂SO₄, filtered, and the solvents were evaporated in vacuo. The crude product was purified by flash column chromatography (silica gel; petroleum ether/EtOAc, 9:1) to afford 1.6 g of methyl 2-((4-methoxyphenyl)amino)-2-phenylpent-4-ynoate (S25) (64% yield) as a yellow oil. Rf = 0.23 (petroleum ether/EtOAc, 9:1); ¹H NMR (400 MHz, CDCl₃) δ 2.02 (t, J = 2.6 Hz, 1H), 3.21 (dd, J = 16.4, 2.6 Hz, 1H), 3.39 (dd, J = 16.4, 2.6 Hz, 1H), 3.69 (s, 3H), 3.72 (s, 3H), 4.97 (s, 1H), 6.36 – 6.46 (m, 2H), 6.58 – 6.70 (m, 2H), 7.30 – 7.43 (m, 3H), 7.52 – 7.62 (m, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 25.0, 53.3, 55.6, 66.9, 71.9, 79.4, 114.5, 118.8, 127.0, 128.2, 128.9, 137.8, 139.7, 153.3, 173.1; HRMS (ESI): m/z calcd for C₁₉H₂₀NO₃ [M+H]⁺: 310.1443; found: 310.1430.

---

⁵G. Shang, Q. Yang, X. Zhang, *Angew. Chem. Int. Ed.* 2006, 45, 6360.
A solution of CAN (3.78 g, 6.9 mmol) in water (22 mL) was added drop-wise over 15 minutes to a stirred solution of S25 (1.067 g, 3.45 mmol) in MeCN (22 mL) cooled to 0 ºC. After 2 hours stirring, the resulting solution was treated with 2N HCl to achieve pH 1. The aqueous phase was washed with EtOAc (3x) and basified by the addition of K₂CO₃. The resulting suspension was extracted with CH₂Cl₂ (3x), dried over Na₂SO₄, filtered, and the solvents were evaporated under reduced pressure to yield 450 mg of 1' (64% yield) as a colourless oil without further purification. 

RF = 0.32 (petroleum ether/EtOAc, 2:1); ¹H NMR (400 MHz, CDCl₃) δ 2.06 (t, J = 2.6 Hz, 1H), 2.18 (br s, 2H), 2.77 (dd, J = 16.4, 2.6 Hz, 1H), 3.14 (dd, J = 16.4, 2.6 Hz, 1H), 3.76 (s, 3H), 7.27 – 7.33 (m, 1H), 7.33 – 7.40 (m, 2H), 7.48 – 7.55 (m, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 31.1, 53.0, 63.5, 71.6, 80.0, 125.4, 128.1, 128.7, 141.5, 174.9; HRMS (EI): m/z calcd for [C₁₂H₁₄NO₂]⁺: 204.1021; found: 204.1025.

**Synthesis of methyl 2-((tert-butoxycarbonyl)amino)-2-phenylpent-4-ynoate (S2')**

Boc₂O (642 mg, 2.94 mmol) was added to a solution of 1' (200 mg, 0.98 mmol) in THF (10 mL) and the resulting mixture was stirred at 70 ºC overnight (in a sealed tube). Then, the solvent was evaporated under reduced pressure and the crude product was purified by column chromatography (silica gel; petroleum ether/EtOAc, 4:1) to yield 249 mg of S2' (84% yield) as a white solid. 

RF = 0.22 (petroleum ether/EtOAc, 8:1); mp 100 – 102 ºC; ¹H NMR (400 MHz, CDCl₃) δ 1.41 (br s, 9H), 1.99 (s, 1H), 3.45 (dd, J = 16.2, 1.7 Hz, 1H), 3.57 (br s, 1H), 3.71 (s, 3H), 6.04 (s, 1H), 7.27 – 7.40 (m, 3H), 7.41 – 7.46 (m, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 25.3, 28.4, 53.5, 64.5, 71.3, 79.6, 80.2, 125.9, 128.3, 128.7, 138.5, 154.1, 171.9; HRMS (EI): m/z calcd for [C₁₇H₂₁NO₄Na]⁺: 326.1368; found 326.1365.
Synthesis of methyl 7-oxo-5-phenyl-5,6,7,8-tetrahydro-4H-[1,2,3]triazolo[1,5-d][1,4]diazepine-5-carboxylate (10')

A solution of S2' (100 mg, 0.32 mmol) and ethyl 2-azidoacetate (62 mg, 0.48 mmol) in toluene (1.6 mL) was degassed for 15 minutes with argon. Cp*RuCl(COD) (2.3 mg, 0.006 mmol) was added and the mixture was stirred at 80 ºC for 1 hour. Then, the solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (silica gel; petroleum ether/EtOAc, 1:1) to yield 120 mg of methyl 2-((tert-butoxycarbonyl)amino)-3-(1-(2-ethoxy-2-oxoethyl)-1H-1,2,3-triazol-5-yl)-2-phenylpropanoate (S9') (87% yield) as a colourless oil. Rf = 0.18 (petroleum ether/EtOAc; 2:1); 1H NMR (400 MHz, CDCl3) δ 1.25 (t, J = 7.1 Hz, 3H), 1.38 (s, 9H), 3.74 (s, 3H), 3.86 (d, J = 15.0 Hz, 1H), 4.02 (d, J = 15.2 Hz, 1H), 4.11 – 4.28 (m, 2H), 4.84 (d, J = 17.7 Hz, 1H), 5.09 (d, J = 17.7 Hz, 1H), 5.85 (s, 1H), 7.19 (s, 1H), 7.28 – 7.41 (m, 5H); 13C NMR (101 MHz, CDCl3) δ 14.1, 28.2, 29.2, 48.7, 53.6, 62.3, 65.1, 80.9, 125.3, 128.7, 129.1, 133.5, 133.6, 138.4, 154.6, 166.6, 171.8; HRMS (EI): m/z calcd for C21H28N4NaO6 [M+Na]+: 455.1907; found: 455.1901.

TFA (0.6 mL) was added to a solution of S9' (70 mg, 0.16 mmol) in CH2Cl2 (1 mL) and after 2 hours stirring the solvent was removed under reduced pressure. The crude product was dissolved in EtOAc and a saturated aqueous solution of NaHCO3 was added and the mixture was stirred for 10 minutes. Then, the organic layer was separated, dried over Na2SO4,
filtered and concentrated in vacuo to afford 53 mg methyl 2-amino-3-(1-(2-ethoxy-2-oxoethyl)-1H-1,2,3-triazol-5-yl)-2-phenylpropanoate (8') (quantitative yield) as a colourless oil without further purification. \( R_f = 0.28 \) (petroleum ether:EtOAc; 1:2); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 1.26 (t, \( J = 7.1 \) Hz, 3H), 1.95 (s, 2H), 3.19 (d, \( J = 15.0 \) Hz, 1H), 3.51 (d, \( J = 15.0 \) Hz, 1H), 3.72 (s, 3H), 4.21 (q, \( J = 7.1 \) Hz, 2H), 5.08 (d, \( J = 17.6 \) Hz, 1H), 5.16 (d, \( J = 17.6 \) Hz, 1H), 7.29 – 7.40 (m, 4H), 7.40 – 7.46 (m, 2H); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 1.26 (t, \( J = 7.1 \) Hz, 3H), 1.95 (s, 2H), 3.19 (d, \( J = 15.0 \) Hz, 1H), 3.51 (d, \( J = 15.0 \) Hz, 1H), 3.72 (s, 3H), 4.21 (q, \( J = 7.1 \) Hz, 2H), 5.08 (d, \( J = 17.6 \) Hz, 1H), 5.16 (d, \( J = 17.6 \) Hz, 1H), 7.29 – 7.40 (m, 4H), 7.40 – 7.46 (m, 2H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \( \delta \) 14.2, 34.4, 49.2, 53.0, 62.3, 64.3, 125.1, 128.5, 129.0, 133.6, 134.4, 141.6, 166.8, 174.6; HRMS (EI): m/z calcd for C\(_{16}\)H\(_{21}\)N\(_4\)O\(_4\) [M+H]\(^+\): 333.1563; found: 333.1560.

A stirred solution of 8' (38 mg, 0.11 mmol) in toluene (3.8 mL) was heated at 150 °C overnight. Then, the solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (silica gel; EtOAc) to afford 24 mg of 10' (76% yield) as a colourless oil. \( R_f = 0.29 \) (EtOAc); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 3.62 (d, \( J = 16.6 \) Hz, 1H), 3.78 (s, 3H), 4.20 (d, \( J = 16.6 \) Hz, 1H), 4.61 (d, \( J = 16.7 \) Hz, 1H), 5.20 (d, \( J = 16.7 \) Hz, 1H), 7.27 – 7.37 (m, 5H), 7.40 (br s, 1H), 7.48 (s, 1H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \( \delta \) 31.0, 53.3, 54.4, 64.3, 125.6, 129.5, 129.7, 131.3, 134.1, 137.2, 165.1, 170.4; HRMS (ESI): m/z calcd for C\(_{14}\)H\(_{15}\)N\(_4\)O\(_3\) [M+H]\(^+\): 287.1139; found: 287.1135.
SYNTHESIS OF THE OPTICALLY PURE DERIVATIVE (R)-22

Synthesis of methyl (R)-2-amino-2-methylpent-4-ynoate ((R)-1)

Propargyl bromide (0.62 mL, 8.11 mmol) and activated zinc powder (530 mg, 8.11 mmol) were added to a solution of (R)-3-methyl-5-phenyl-5,6-dihydro-2H-1,4-oxazin-2-one (1.03 g, 5.41 mmol) in DMF (27 mL) and the mixture was stirred for 1 hour and at 60 °C for 2 hours. Then, the mixture was cooled to 0 °C and hydrolysed with a saturated aqueous solution of NH₄Cl. The aqueous layer was extracted with EtOAc (3x), washed with brine, dried over Na₂SO₄, filtered, and the solvents were evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel; petroleum ether/EtOAc, 8:1) to afford 930 mg of (3R,5R)-3-methyl-5-phenyl-3-(prop-2-yn-1-yl)morpholin-2-one (S28) (75% yield) as an inseparable mixture of regioisomers (mixture of S28 and inconsequential allene, ca. 82:18 ratio as determined by ¹H NMR). Rᵣ = 0.18 (petroleum ether/EtOAc, 8:1); [α]²⁵D +42.4 (c 0.6, CHCl₃); spectroscopic data of the major regioisomer (S28): ¹H NMR (400 MHz, CDCl₃) δ 1.59 (s, 3H), 2.11 (t, J = 2.6 Hz, 1H), 2.37 (br s, 1H), 2.65 (dd, J = 16.9, 2.6 Hz, 1H), 3.12 (dd, J = 16.9, 2.5 Hz, 1H), 4.30 – 4.36 (m, 3H), 7.38 – 7.48 (m, 3H), 7.45 – 7.49 (m, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 26.7, 28.7, 53.2, 59.0, 73.0, 75.4, 78.5, 127.4.

---

⁶ L. M. Harwood, K. J. Vines, M. G. B. Drew, Synlett 1996, 1051.
⁷ Some examples on the use of chiral iminolactones derived from phenylglycinol in diastereoselective syntheses: a) L. M. Harwood, S. N. G. Tyler, G. B. Drew, A. Jahans, Arkivoc 2000, 820; b) S. Fustero, N. Mateu, A. Simón-Fuentes, J. L. Aceña, Org. Lett. 2010, 12, 3014; c) S. Fustero, N. Mateu, L. Albert, J. L. Aceña, J. Org. Chem. 2009, 74, 4429.
SO₂Cl (0.6 mL, 8.1 mmol) was added drop-wise to a solution of S28 (930 mg, 4.05 mmol) in MeOH (40 mL). The mixture was stirred for 2 hours and then the solvent was removed under reduced pressure. The resulting residue was dissolved in EtOAc and a saturated aqueous solution of NaHCO₃. The mixture was stirred for 15 minutes and then the aqueous layer was separated and extracted with EtOAc (2x). The combined organic layers were dried over Na₂SO₄, filtered, and the solvents were evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel; petroleum ether/EtOAc, 2:1) to afford 887 mg of methyl (R)-2-(((R)-2-hydroxy-1-phenylethyl)amino)-2-methylpent-4-ynoate (S29) (84% yield) as a colourless oil. [α]²⁵_D –72.8 (c 0.9, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 1.40 (s, 3H), 1.99 (t, J = 2.6 Hz, 1H), 2.29 (s, 1H), 2.49 (qd, J = 16.6, 2.6 Hz, 2H), 3.02 (s, 1H), 3.37 (s, 3H), 3.38 – 3.48 (m, 1H), 3.56 (dd, J = 10.9, 4.4 Hz, 1H), 3.82 (dd, J = 9.3, 4.7 Hz, 1H), 7.20 – 7.27 (m, 3H), 7.27 – 7.34 (m, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 22.6, 30.0, 52.1, 59.8, 60.9, 67.0, 71.4, 79.9, 127.2, 127.7, 128.6, 141.1, 174.9; HRMS (ESI): m/z calcd for C₁₅H₁₉NNaO₃ [M+Na]⁺: 284.1257; found: 284.1246.

Pb(OAc)₄ (1.184 g, 2.67 mmol) was added to a solution of S29 (500 mg, 1.91 mmol) in a mixture 2:1 of CH₂Cl₂:MeOH (18 mL) at 0 ºC. The reaction mixture was vigorously stirred for 1 hour at 0 ºC, and then 20 mL of 2M HCl were added. The reaction was warmed to room temperature and after 2 hours of additional stirring the reaction mixture was filtered through a pad of SiO₂, eluting with MeOH. The organic solvents were removed under reduced pressure and the aqueous residue was washed with EtOAc (3x) and basified by the addition of Na₂CO₃. The resulting suspension was extracted with EtOAc (3x), dried over Na₂SO₄, filtered and the solvents were evaporated under reduced pressure to yield 232 mg of (R)-1 (85% yield) as a colourless oil without further purification. [α]²⁵_D +16.1 (c 0.2, CHCl₃) (lit. data: [α]²⁵_D +2.08 (c 0.8, ethanol).”) The spectroscopic data are in agreement with those
previously reported in the literature.\(^2\) HRMS (ESI): \(m/z\) calcd for \(\text{C}_7\text{H}_{12}\text{NO}_2\) \([\text{M+H}]^+\): 142.0863; found: 142.0866.

**Synthesis of methyl (\(R\))-2-((\text{\textit{tert}-butoxycarbonyl})amino)-2-methylpent-4-ynoate ((\(R\))-S2)**

\[
\begin{align*}
\text{\(\text{\(R\)}\)-1} & \quad \xrightarrow{\text{Boc}_2\text{O}} \quad \text{\(\text{\(R\)}\)-S2} \\
\end{align*}
\]

\(\text{Boc}_2\text{O} (478 \text{ mg, } 2.19 \text{ mmol})\) was added to a solution of (\(\text{\(R\)}\)-1) (155 \text{ mg, } 1.1 \text{ mmol}) in THF (5.5 \text{ mL}) and the resulting mixture was stirred at 70 °C overnight (in a sealed tube). Then, the solvent was evaporated under reduced pressure and the crude product was purified by column chromatography (silica gel; petroleum ether/EtOAc, 4:1) to yield 238 \text{ mg} of (\(\text{\(R\)}\)-S2) (90% yield) as a white solid. \([\alpha]^{25}_{\text{D}} +34.1 \ (c \ 0.7, \text{CHCl}_3)\) (lit. data for (\(S\))-\(\text{\textit{N}}\)-\(\text{\textit{Boc}}\)-\(\alpha\)-propargylalanine methyl ester: \([\alpha]^{25}_{\text{D}} –63 \ (c \ 0.10, \text{THF})\). The spectroscopic data are in agreement with those previously reported in the literature for the (\(S\))-\(\text{\textit{N}}\)-\(\text{\textit{Boc}}\)-\(\alpha\)-propargylalanine methyl ester.\(^3\) HRMS (ESI): \(m/z\) calcd for \(\text{C}_{12}\text{H}_{20}\text{NO}_4\) \([\text{M+H}]^+\): 242.1392; found: 242.1382.

**Synthesis of methyl (\(R\))-5-methyl-7-oxo-5,6,7,8-tetrahydro-4\(H\)[1,2,3]triazolo[1,5-\(d\)][1,4]diazepine-5-carboxylate ((\(R\))-10)**

\[
\begin{align*}
\text{\(\text{\(R\)}\)-S2} & \quad \xrightarrow{\text{N}_3\text{CO}_2\text{Et}, \text{Cp}^*\text{RuCl(COD)} \text{PhMe, 50 °C, 1h}} \quad \text{\(\text{\(R\)}\)-S9} \\
\text{\(\text{\(R\)}\)-S9} & \quad \xrightarrow{\text{TFA, DCM, rt, 2h then NaHCO}_3} \quad \text{\(\text{\(R\)}\)-8} \\
\text{\(\text{\(R\)}\)-8} & \quad \xrightarrow{\text{PhMe 150 °C, 66h}} \quad \text{\(\text{\(R\)}\)-10} \\
\end{align*}
\]
A solution of \((R)-\text{S2}\) (100 g, 0.41 mmol) and ethyl 2-azidoacetate (80 mg, 0.62 mmol) in toluene (2.4 mL) was degassed for 15 minutes with argon. \(\text{Cp}^*\text{RuCl(COD)}\) (3.8 mg, 0.01 mmol) was added and the mixture was stirred at 50 °C for 1 hour. Then, the solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (silica gel; petroleum ether/EtOAc, gradient from 1:1 to 1:2) to yield 116 mg of \((R)-2-(((\text{tert-butoxycarbonyl})\text{amino})-3-(1-(2-ethoxy-2-oxoethyl)-1H-1,2,3-triazol-5-yl)-2-methylpropanoate \((R)-\text{S9}\) (76% yield) as a colourless oil. \(R_t = 0.25\) (petroleum ether/EtOAc, 1:1); \([\alpha]^{25}_D +7.3\) (c 0.5, CHCl\(_3\)); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 1.25 (t, \(J = 7.1\) Hz, 3H), 1.40 (s, 9H), 3.38 (d, \(J = 15.5\) Hz, 1H), 3.51 (d, \(J = 15.4\) Hz, 1H), 3.76 (s, 3H), 4.20 (q, \(J = 7.1\) Hz, 2H), 5.12 (s, 2H), 5.30 (s, 1H), 7.40 (s, 1H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 14.1, 24.2, 28.3, 29.3, 48.8, 53.2, 59.2, 62.3, 80.6, 133.5, 133.8, 154.7, 166.6, 173.7; HRMS (ESI): \(m/z\) calcd for C\(_{16}\)H\(_{27}\)N\(_4\)O\(_6\) [M+H]\(^+\): 371.1925; found: 371.1921.

TFA (1 mL) was added to a solution of \((R)-\text{S9}\) (136 mg, 0.37 mmol) in CH\(_2\)Cl\(_2\) (2 mL) and after 2 h stirring the solvent was removed under reduced pressure. The crude product was dissolved in EtOAc (2 mL) and a saturated aqueous solution of NaHCO\(_3\) (2 mL) was added and the mixture was stirred for 10 minutes. Then, the organic layer was separated and the aqueous layer extracted with EtOAc (2x). The combined organic layers were dried over Na\(_2\)SO\(_4\), filtered and concentrated in vacuo to afford 92 mg methyl \((R)-2\)-amino-3-(1-(2-ethoxy-2-oxoethyl)-1H-1,2,3-triazol-5-yl)-2-methylpropanoate \((R)-\text{8}\) (93% yield) as a colourless without further purification. \(R_t = 0.22\) (EtOAc); \([\alpha]^{25}_D +9.2\) (c 1.0, CHCl\(_3\)); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 1.27 (t, \(J = 7.1\) Hz, 3H), 1.38 (s, 3H), 1.69 (s, 2H), 2.83 (d, \(J = 14.9\) Hz, 1H), 3.16 (d, \(J = 14.9\) Hz, 1H), 3.72 (s, 3H), 4.22 (q, \(J = 7.1\) Hz, 2H), 5.29 (d, \(J = 17.6\) Hz, 1H), 5.35 (d, \(J = 17.6\) Hz, 1H), 7.49 (s, 1H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 14.2, 27.0, 34.1, 49.5, 52.8, 58.3, 62.3, 133.9, 133.9, 166.9, 176.7; HRMS (EI): \(m/z\) calcd for C\(_{11}\)H\(_{19}\)N\(_4\)O\(_4\) [M+H]\(^+\): 271.1401; found: 271.1396.
A stirred solution of \((R)-8\) (48 mg, 0.17 mmol) in toluene (3 mL) was heated at 150º C for 66 hours. Then, the solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (silica gel; EtOAc 100%) to afford 30 mg of \((R)-10\) (79% yield) as a white solid. \(R_f = 0.18\) (EtOAc 100%); [\(\alpha\)]\textsubscript{25}D = –12.9 (c 0.6, CHCl\(_3\)); mp 147 – 149 ºC; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 1.54\) (s, 3H), 3.34 (d, \(J = 15.8\) Hz, 1H), 3.56 (d, \(J = 15.8\) Hz, 1H), 3.70 (s, 3H), 5.28 (d, \(J = 0.6\) Hz, 2H), 7.54 (s, 1H), 6.83 (br s, 1H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta 27.4, 31.0, 52.7, 53.7, 60.7, 131.9, 133.7, 165.0, 172.1\); HRMS (EI): \(m/z\) calcd for \(C_9H_{13}N_4O_3\) [M+H]\(^+\): 225.0982; found: 225.0982.
STEREOCHEMICAL AND STRUCTURAL ASSIGNMENTS

Compounds 2 and 3

The position of the phenyl substituent present in 2 and 3 was established by means of nOe studies. Thereby, in the nOe spectrum of compound 2 the aromatic proton (H_a) at the α-position to the nitrogen showed an interaction with the methylene group (2H_c) adjacent to the NH (Figure S3). As expected, the nOe spectrum of 3 showed an interaction between the aromatic proton (H_a) at the α-position to the nitrogen and the methylene group (2H_b) adjacent to the quaternary stereocenter (Figure S4).

Figure S3.
Compound 14

Attempts to determine the relative position of the substituents present within 14 were carried out. Unfortunately, nOe experiments were not conclusive however, further analysis is being carried out to determine the relative configuration of 14.

Compound 16

The relative position of the substituents present in 16 was established by means of nOe studies. Thereby, in the nOe spectrum of compound 16, the alkene proton (Hₐ) showed an interaction with the NH proton (Hₖ) (Figure S6). Furthermore, an interaction could also be seen between the alkene proton (Hₐ) and the t-butyl group methyl groups Hₖ).
Figure S6.
COMPUTATIONAL ANALYSIS

A) Principal Moment of Inertia (PMI)

General details

Principal Moment of Inertia (PMI) was performed using Molecular Operating Environment (MOE) software package version 2012.10 from the Chemical Computing Group. Merck molecular force field 94X (MMFF94x), an all-atom force field parameterised for small organic molecules with the Generalised Born solvation model, was used to minimise the energy potential of the library members. A LowModeMD search was employed for the conformation generation. Detailed settings for conformational search are listed below.

| Setting            | Value  |
|--------------------|--------|
| Rejection Limit    | 100    |
| RMS Gradient       | 0.005  |
| Iteration Limit    | 10000  |
| MM Iteration Limit | 500    |
| RMSD Limit         | 0.15   |
| Energy window      | 3      |
| Conformation Limit | 100    |

Only the conformer with the lowest energy was retained for principal moment of inertia (PMI) calculations. Normalized PMI ratios (I1/I3 and I2/I3) of these conformers were obtained from MOE and then plotted on a triangular graph, with the canonical coordinates (0,1), (0.5,0.5) and (1,1) representing a perfect rod, disc and sphere respectively (Figure 3).

Compound collections analysed and PMI plots

Collection 1: DOS Library based on reported 40 small molecules.
Table S1. Chemical structures of DOS Library in SMILES format.

| Compound | SMILES |
|----------|--------|
| 2        | O=C(C1(C)CC2=C(C=NC(C3=CC=CC3)=C2)CN1)OC |
| 3        | O=C(C1(C)CC2=C(C=C(C3=CC=CC3)N=C2)CN1)OC |
| 4        | C=C(CC(C(OC)=O)(C)N1)OC1=O |
| 5        | O=C1N(C)C(C(OC)=O)(C)CC2=CN=NN2C3=C1C=CC=C3 |
| 6        | O=C1C=C(C)NC(C)(C(OC)=O)C1 |
| 7        | NC(C)(C(OC)=O)CC1=CON=C1C(OC)=O |
| 8        | NC(C1=CN=NN1CC(OC)=O)(C)C(OC)=O |
| 9        | O=C1NC(C)(C(OC)=O)CC2=CON=C21 |
| 10       | O=C(CN1C(C2)=CN=N1)NC2(C(OC)=O)C |
| 11       | NC(C1=CN=NN1C2=CC=CC=C2)(C)C(OC)=O |
| 12       | NC(C1=CN(C2=CC=CC=C2)N=N1)(C(OC)=O)C |
|   | Chemical Structure                                                                 |
|---|------------------------------------------------------------------------------------|
| 13| NC(CCCC1=CC=CC=C1C(O)=O)(C)(OC)=O                                                  |
| 14| CC(C1)(NC(OC(C)(C))=O)OC(C2C1=CCN(C3=CC=CC=C3)O2                                  |
| 15| CC1(NC(C)=O)OC(C2=C(C)N=C(C3=CC=CC=C3)C=C2C1                                      |
| 16| O=C(N1C)[C@]([C@@][2([H])C1=O][([H])CC=C3[C@@@H]2OCC[C@](N(C=C)(O)(C)](C3)C3)    |
| 17| O=C1C(NC(OC(C)(C))=O)(C)CC(O1)=C                                                   |
| 18| CC1(NC(OC(C)(C))=O)OC=CC1                                                          |
| 19| C#CCC(C)(C(OC)=O)N1C=CC=C1                                                         |
| 21| O=C(N(C)C1(CC#C)C)C2=C(C=CC=C2)NC1=O                                               |
| 22| O=C(NC1(CC#C)C)CC1=O                                                              |
| 23| C#CCC1(C)N(C(OC(C)(C))=O)C1                                                        |
| 24| C#CCC(CO1)(C)NCC1=O                                                               |
| 25| O=C1OCC(CC#C)(C)N1                                                               |
| 26| C#CCC(CO1)(C)NC1=O                                                               |
| 27| O=C1C(N2C=CC=C2)(C)CC(O1)=C                                                        |
| 28| CC1(C(OC)=O)OC=CC2=CC=CN12                                                        |
| 29| O=C(C1(C)CC2=CC=C(C3CC3)N=C2C4=CC=CN14)OC                                          |
| 30| O=C(C1(C)CC2=CC=C(C3CC3)N=C2C4=CC=CN14)OC                                          |
| 31| O=C(NC1)(C)(CCC)N2C1=CC=C2                                                         |
| 32| O=C1OCC2(C)N1C=CC2                                                               |
| 33| O=C1OCC2(C)N1C=CC2                                                               |
| 19a| CC(C1=CN(C2=CC=CC=C2)N=N1)(C(OC)=O)N3C=CC=C3                                       |
| 21a| O=C(N(C)C1(CC2=CN(C3=CC=CC=C3)N=N2)C4=C(C=CC=C4)NC1=O                           |
| 22a| O=C(NC1(CC2=CN(C3=CC=CC=C3)N=N2)C)CC1=O                                           |
| 26a| O=C1OCC2(C)N1C=CC2=CN(C3=CC=CC=C3)N=N2)(C)N1                                      |
Table S2. Normalised PMI ratio (npr) values of conformers of the DOS Library with the lowest energy.

| Compound | npr1  | npr2  |
|----------|-------|-------|
| 2        | 0.2007| 0.9149|
| 3        | 0.1761| 0.9628|
| 4        | 0.6608| 0.9315|
| 5        | 0.4033| 0.7284|
| 6        | 0.348 | 0.7927|
| 7        | 0.2989| 0.8118|
| 8        | 0.3747| 0.7195|
| 9        | 0.2735| 0.8451|
| 10       | 0.3122| 0.813 |
| 11       | 0.3506| 0.7691|
| 12       | 0.1877| 0.9268|
| 13       | 0.4495| 0.9293|
| 14       | 0.3226| 0.8555|
| 15       | 0.2727| 0.8894|
| 16       | 0.2417| 0.9216|
| 17       | 0.2034| 0.9381|
| 21b      | O=C(N(C)C1(CC#CC2=CC=CC=C2)C3=C(C=CC=C3)NC1=O|
| 22b      | O=C(NC1(CC#CC2=CC=CC=C2)C)CC1=O|
| 21c      | O=C(N(C)C1(CCC)C2=C(C=CC=C2)NC1=O|
| 22c      | O=C(NC1(C)CCC)CC1=O|
| 23d      | O=C(OCC)CN1C(CC2(C)N(C(OC(C)(C)C)=O)C2)=CN=N1|
|    | 18   | 0.2626 | 0.9435 |
|----|------|--------|--------|
|    | 19   | 0.646  | 0.695  |
|    | 21   | 0.5321 | 0.8555 |
|    | 22   | 0.4319 | 0.7592 |
|    | 22b  | 0.1535 | 0.9378 |
|    | 21c  | 0.6047 | 0.9251 |
|    | 22c  | 0.538  | 0.8653 |
|    | 23d  | 0.3812 | 0.8038 |

**Figure S7.** PMI plot of DOS Library.

**Collection 2: DOS Library Ph.** Virtual collection of 40 small molecules based on DOS Library featuring a Ph substituent at the quaternary stereocenter.
Table S3. Chemical structures of DOS Library Ph in SMILES format.

| Compound | SMILES |
|----------|---------|
| 2'       | O=C(C1(C2=CC=CC=C2)CC3=C(C=NC(C4=CC=CC=C4)=C3)CN1)OC |
| 3'       | O=C(C1(C2=CC=CC=C2)CC3=C(C=C(C4=CC=CC=C4)N=C3)CN1)OC |
| 4'       | C=C(C(C(CC(C(OC)=O)(C1=CC=CC=C1)N2)OC2=O |
| 5'       | O=C1N(C(C(C(OC)=O)(C2=CC=CC=C2)CC3=CN=NN3C4=C1C=CC=C |
| 6'       | O=C1NC=C(C(C2=CC=CC=C2)(C(OC)=O)C1 |
| 7'       | NC(C1=CC=CC=C1)(C(OC)=O)CC2=CON=C2C(OC)=O |
| 8'       | NC(CC1=CN=NN1CC(OC)C=O)(C2=CC=CC=C2)C(OC)=O |
| 9'       | O=C1NC(C2=CC=CC=C2)(C(OC)=O)CC3=CON=C31 |
| 10'      | O=C(CN1C(C2)=CN=N1)NC2(C(OC)=O)C3=CC=CC=C3 |
|   |   |
|---|---|
| 11' | NC(CC1=CN=NN1C2=CC=CC=C2)(C3=CC=CC=C3)C(OC)=O |
| 12' | NC(CC1=CN(C2=CC=CC=C2)N=N1)(C(OC)=O)C3=CC=CC=C3 |
| 13' | NC(CCCC1=CC=CC=C1C(O)=O)(C2=CC=CC=C2)C(OC)=O |
| 14' | CC(CC1=CN=NN1C2=CC=CC=C2)COCC3C1=CCN(C4=CC=CC=C4)O3 (=O)(C)C |
| 15' | CC1=C(COCC(NC(C)=O)(C2=CC=CC=C2)C3)C3=CC(C4=CC=CC=C4 )=N1 |
| 16' | O=C(N1O)[C@]([C@@]2([H])C1=O)([H])CC=C3[C@]@H[2OC[C@]1(N C(C)=O)(C4=CC=CC=C4)C3 |
| 17' | O=C1C(NC(OC(C)(C)C)=O)(C2=CC=CC=C2)CC(O1)=C |
| 18' | CC(OC(NC1(C2=CC=CC=C2)COC=CC1)=O)(C)C |
| 19' | C#CCC(C1=CC=CC=C1)(C(OC)=O)N2C=CC=C2 |
| 21' | O=C(N(C)C1(CC#C)C2=CC=CC=C2)C3=C(C=CC=C3)NC1=O |
| 22' | O=C(1C1(CC#C)C2=CC=CC=C2)CC1=O |
| 23' | C#CCC1(C2=CC=CC=C2)N(C(OC(C)(C)C)=O)C1 |
| 24' | C#CCC(CO1)(C2=CC=CC=C2)NCC1=O |
| 25' | O=C1OCC(CC#C)(C2=CC=CC=C2)N1 |
| 26' | C#CCC(CO1)(C2=CC=CC=C2)NC1=O |
| 27' | O=C1C(N2C=CC=C2)(C3=CC=CC=C3)CC(O1)=C |
| 28' | O=C(C1(C2=CC=CC=C2)CC3=CC=CC=CN13)OC |
| 29' | O=C(C1(C2=CC=CC=C2)CC3=CC=C(C4CC4)N=C3C5=CC=CN15)OC |
| 30' | O=C(C(C1(C2=CC=CC=C2)CC3=CC(C4CC4)=CN=C3C5=CC=CN15)OC |
| 31' | O=C(C(C1(C2=CC=CC=C2)CC3=CC=CC=C3)N3C1=CC=C3 |
| 32' | O=C1OCC2(C3=CC=CC=C3)N1C=CC=C2 |
| 33' | O=C1OCC2(C3=CC=CC=C3)N1C=CC=C2 |
| 19a' | O=C(C(CC1=CN(C2=CC=CC=C2)N=N1)(C3=CC=CC=C3)N4C=CC=C4 )OC |
### Table S4. Normalised PMI ratio (npr) values of conformers of the DOS Library Ph with the lowest energy.

| Compound | npr1   | npr2   |
|----------|--------|--------|
| 2'       | 0.2509 | 0.2509 |
| 3'       | 0.2509 | 0.932  |
| 4'       | 0.4634 | 0.9343 |
| 5'       | 0.6252 | 0.7811 |
| 6'       | 0.6827 | 0.7967 |
| 7'       | 0.4118 | 0.4118 |
| 8'       | 0.4118 | 0.8226 |
| 9'       | 0.5677 | 0.773  |
| 10'      | 0.606  | 0.8234 |
| 11'      | 0.496  | 0.8478 |
| 12'      | 0.3317 | 0.8011 |
| 13'      | 0.3531 | 0.8914 |
| 21a'     | O=C(N(C)C1(CC2=CN(C3=CC=CC=C3)N=N2)C4=CC=CC=C4)C5=C(C=CC=C5)NC1=O |
| 22a'     | O=C(NC1(CC2=CN(C3=CC=CC=C3)N=N2)C4=CC=CC=C4)CC1=O |
| 26a'     | O=C1OCC(CC2=CN(C3=CC=CC=C3)N=N2)(C4=CC=CC=C4)N1 |
| 21b'     | O=C(N(C)C1(CC#CC2=CC=CC=C2)C3=CC=CC=C3)C4=C(C=CC=C4)NC1=O |
| 22b'     | O=C(NC1(CC#CC2=CC=CC=C2)C3=CC=CC=C3)CC1=O |
| 21c'     | O=C(N(C)C1(CCC)C2=CC=CC=C2)C3=C(C=CC=C3)NC1=O |
| 22c'     | O=C(NC1(C2=CC=CC=C2)CCC)CC1=O |
| 23d'     | O=C(OCC)CN1C(C2(CC=CC=C3)N(C(OC(C)(C))=O)C2)=CN=N |

| Compound | npr1   | npr2   |
|----------|--------|--------|
| 23       | 0.3872 | 0.7793 |
| 24'      | 0.5471 | 0.754  |
| 25'      | 0.3858 | 0.7454 |
| 26'      | 0.4475 | 0.7587 |
| 27'      | 0.5158 | 0.8271 |
| 28'      | 0.643  | 0.784  |
| 29'      | 0.3867 | 0.9416 |
| 30'      | 0.4424 | 0.9206 |
| 31'      | 0.5641 | 0.6922 |
| 32'      | 0.5096 | 0.9404 |
| 33'      | 0.3555 | 0.8412 |
| 19a'     | 0.2371 | 0.9147 |
Figure S8. PMI plot of DOS Library Ph.
Collection 3: Maybridge ‘Ro3’ core fragment collection

This library is based on the core 1000-member collection within the Maybridge Fragment library. Details of the library (including SMILES and SDF) are available from ‘http://www.maybridge.com/’ under the ‘Ro3 Fragment library section. More details can be found at:

‘http://www.maybridge.com/images/pdfs/MB_Ro3_fragment_flyer_2011_EUR_v7.pdf’

Figure S9. PMI plot of Maybridge ‘Ro3’ core collection.
Figure S10. Comparative PMI plot of the presented DOS library, the virtual DOS Library Ph and the Maybridge ‘Ro3’ core collection.

Analysis of comparative PMI plot

Figure S9 shows that the synthesized DOS Library displays a high level of molecular shape diversity, covering a broad area of molecular shape space. Notable differences in the molecular shape space distribution can be observed between the DOS library and the DOS Library Ph, with a shift towards the right-hand side of the plot. In comparison to the Maybridge ‘Ro3’ core fragment collection, the DOS library presented in this work shows a broader coverage of the 3D molecular space shape, whilst the Maybridge library is densely populated around the ‘rod-’ and ‘disk-’ like areas of the plot. Furthermore, a higher percentage of the DOS Library and DOS Library Ph occupy the right-hand side of the plot suggesting more 3D character, when compared to the Maybridge library.
B) Computational evaluation of physicochemical properties

General details

Computational analysis was carried out using the same MOE software package and settings described above in section A. The DOS 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).

The distribution of these data and the mean values are displayed in a series of histograms in Figure S11. By means of comparison with existing libraries, the mean values are shown alongside those of two popular commercially available fragment libraries, Chembridge (consisting of 7,547 fragments) and Maybridge ‘Ro3’ core collection (consisting of 1,000 fragments), in Table 1.
Figure S11. Histograms showing the distribution of predicted physicochemical properties for compounds in the DOS library.
C) Multi-Dimensional Scaling (MDS) Plot Generation

Selection of ChEMBL 20 compounds

All compounds reported as ligands of kinases (80,999), proteases (106,953), hydrolases (35,606), ion channels (51,182), membrane receptors (299,374), transporters (39,669), and transcription factors (136,557) were extracted from the ChEMBL 20 database, followed by molecular weight filtering (200-700) and removal of salts using KNIME 2.11.3. The KNIME workflow filtered the compounds in the following sequence: It (a) read the chemical data from the SDF file (b) calculated the RDKit descriptor (M.W.) (c) applied the molecular weight filters via the Java snippet node (d) returned the data within the accepted range of molecular weights via the numeric row splitter node and finally (e) removed salts from the filtered compounds using the RDKit salt stripper node. Compounds of each bioactivity class passing all the applied filters, namely ligands of kinases (78,465 structures), proteases (75,504), hydrolases (33,877), ion channels (47,912), membrane receptors (170,461), transporters (37,730), and transcription factors (133,863), were written into separate SDF files.

Multi-Dimensional Scaling (MDS) analysis

2,000 ChEMBL compounds with IC$_{50}$, EC$_{50}$ and $K_i$ values ≤ 10 µM were randomly selected from each bioactivity class for MDS analysis. In addition, compounds synthesized via two different targeted approaches were used as a benchmark, namely those previously presented by Hergenrother (88 compounds), and Kiessling (9 compounds). For this purpose, the SDF files of all compounds belonging to the different bioactivity classes as well as the synthetic libraries and the DOS library presented were standardized using the

---

8 A. Gaulton, L. J. Bellis, A. P. Bento, J. Chambers, M. Davies, A. Hersey, Y. Light, S. McGlinchey, D. Michalovich, B. Al-Lazikani, et al., *Nucleic Acids Res.*, 2011, 40, 1.
9 M. Berthold, N. Cebron, F. Dill, *SIGKDD Explor.*, 2008, 11, 26.
10 http://www.rdkit.org
11 V. Nesterenko, K. S. Putt, P. J. Hergenrother, *J. Am. Chem. Soc.*, 2003, 125, 14672.
12 M. C. Schuster, D. A. Mann, T. J. Buchholz, K. M. Johnson, W. D. Thomas, L. L. Kiessling, *Org. Lett.*, 2003, 5, 1407.
ChemAxon Command-Line Standardizer where the following options were selected: “Remove Fragment” (keep largest), “Neutralize”, “RemoveExplicitH”, “Clean2D”, “Mesomerize” and “Tautomerize”.\(^\text{13}\)

Subsequently, Morgan fingerprints (radius 2, 1024 bits) were generated for all the compounds using KNIME 2.11.3. The workflow generated Morgan fingerprints in the following sequence: It (a) read chemical data from an SDF file, (b) generated RDKit molecules from a molecule string representation and appended them to a table, (c) generated hashed bit-based fingerprints for an input RDKit Mol column and appended them to a table, (d) converted RDKit molecules into string based molecule representations (SMILES), (e) excluded columns from the input table, (f) renamed columns and finally (g) saved the resulting data table into a CSV file.

Using the generated Morgan fingerprints, a 2D-similarity matrix based on Euclidean distance was calculated using R.\(^\text{14}\) Then, a metric multidimensional scaling of the similarity matrix was computed by embedding it into two dimensions (k=2). Subsequently, a two-dimensional plot was obtained labelling the x-axis and the y-axis with Dimension 1 and Dimension 2 respectively, which are two unit less and relative dimensions that recapitulate the pairwise similarity between all points observed in an underlying distribution of Euclidean distances in a higher dimensional space. For each data set in the obtained plot (corresponding to each of the synthetic libraries and bioactivity classes), 90% confidence ellipses were computed using the ellipse package.\(^\text{15}\) Finally, an MDS plot with 90% ellipse-like confidence regions was obtained using R ggplot2 package.\(^\text{16}\)

**NMR SPECTRA**

---

\(^{13}\) L. H. Mervin, A. M. Afzal, G. Drakakis, R. Lewis, O. Engkvist, A. Bender, *J. Cheminform.* 2015, 7, 1.

\(^{14}\) R Core Team. *R: A Language and Environment for Statistical Computing* (version 3.2.4), 2016.

\(^{15}\) D. J. Murdoch, E. D. Chow, *Am. Stat.* 1996, 50, 178.

\(^{16}\) Hadley Wickham, *ggplot2: Elegant Graphics for Data Analysis*, 2009.
11
S18
S18
S22
S24
22b
21c
$S_2'$
(R)-8

\[
\begin{array}{c}
\text{EtO}_2\text{C} \\
\text{N} = \text{N} \\
\text{NH}_2 \\
\text{Me} \\
\text{CO}_2\text{Me}
\end{array}
\]
