Supporting Information (SI)

One-Pot Crabbé Homologation-Radical Cascade Cyclization with Memory of Chirality

Shovan Mondal, a Malek Nechab, a,* Nicolas Vanthuyne, b and Michèle P. Bertrand a,*

a) Institut de Chimie Radicalaire (ICR), UMR 7273
Aix-Marseille Université, Faculté des Sciences St Jérôme, Avenue Escadrille Normandie-Niemen, 13397 Marseille Cedex 20 (France)

E-mail: malek.nechab@univ-provence.fr; michele.bertrand@univ-cezanne.fr

b) Laboratoire de Stéréochimie Dynamique et Chiralité, ISM2, UMR 6263
Aix-Marseille Université, Faculté des Sciences St Jérôme, Avenue Escadrille Normandie-Niemen, 13397 Marseille Cedex 20 (France)

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1. General Information

All reactions were performed under an argon atmosphere using freshly dried solvents. 1,4-Dioxane and Ethyl Acetate were used without any further distillation. THF was distilled over sodium benzophenone ketyl prior to use. Dry state adsorption conditions and purification were performed on silica gel 60 Å (70-230 mesh). Analytical thin layer chromatography was performed on pre-coated silica gel plates. Visualization was accomplished by UV (254 nm) and with phosphomolybdic acid in ethanol. Optical rotations were measured on a Perkin Elmer MC-241 polarimeter using a 10 cm path-length cell at 589 nm. $^1$H and $^{13}$C NMR spectra were recorded on a Bruker Avance III spectrometer (400 MHz and 100 MHz, for $^1$H and $^{13}$C, respectively). Chemical shifts (δ) are reported in ppm and are relative to internal CHCl$_3$ ($^1$H, δ = 7.26) and CDCl$_3$ ($^{13}$C, δ = 77.16). Multiplicity is indicated by one or more of the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad). The lists of coupling constants (J) correspond to the order of multiplicity assignment and are reported in Hertz (Hz). APT was used for $^{13}$C spectra assignment. All melting points were uncorrected and were recorded in open capillary tubes using a Buchi melting point apparatus. High resolution mass spectra were obtained on QStar Elite (Applied Biosystems SCIEX).

Purified compounds were analysed by chiral HPLC with double detection, with UV and circular dichroïsm (CD) detectors. The solvents for chiral chromatography (n-hexane, 2-PrOH, ethanol) were HPLC grade, they were degassed and filtered on a 0.45 µm membrane before use. The columns used are Chiralpak IA or AD-H (250*4.6 mm, amylose tris-(3,5-dimethylphenylcarbamate)), Chiralpak IB or OD-3 (250*4.6 mm, cellulose tris-(3,5-dimethylphenylcarbamate)), Chiralpak IC (250*4.6 mm, cellulose tris(3,5-dichlorophenylcarbamate)) and Lux-Cellulose-4 (250*4.6 mm, cellulose tris(4-chloro,3-methylphenylcarbamate)). Enantiomeric excesses were determined by integration of the peaks on the chromatograms obtained by UV detection at 230, 240 or 254 nm, and confirmed by circular dichroïsm detection at 254 nm. The sign given by the on-line circular dichroïsm detector for one enantiomer is the sign in the solvent used for the chromatographic separation. Retention times Rt in minutes, retention factors $k_i = (Rt_i$-
$Rt_0/Rt_0$, enantioselectivity factor $\alpha = k_2/k_1$ and resolution are given. $Rt_0$ was determined by injection of tri-tertio-butyl benzene.

Iodides 15, 16 and 17 were prepared according to our recently published procedures.\textsuperscript{1} The syntheses of racemic starting materials and of rearranged products were achieved according to the procedures described for optically pure materials in the following. Unless otherwise stated all the yields are isolated yields of pure compounds.

2. Synthesis of iodides 7, 10 and 14

2.1. (S)-Methyl 1-(3-(2-iodophenyl)prop-2-ynyl)pyrrolidine-2-carboxylate (7)

1-Iodo-2-(3-iodoprop-1-ynyl)benzene 5\textsuperscript{1} (2.3 g, 6.25 mmol) was dissolved in DMF (15 mL) and Cs\textsubscript{2}CO\textsubscript{3} (5.1 g, 15.63 mmol) was added followed by L-proline methyl ester hydrochloride 6 (1.24 g, 7.5 mmol), the reaction mixture was stirred for 1 h under argon, poured into water (30 mL), and then extracted with EtOAc (3 x 30 mL). The organic layer was washed with water (2 x 30 mL) and brine (30 mL) and dried over anhydrous sodium sulfate. After evaporation of the solvent, the residue was purified over a short pad of silica gel (pentane/EtOAc, 90/10) to afford 7 as brown oil (1.85 g, 80%).

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) $\delta$: 7.83 (1H, dd, $J = 8.0$ and 0.8, CH\textsubscript{ar}), 7.43 (1H, dd, $J = 7.8$ and 1.5, CH\textsubscript{ar}), 7.29 (1H, td, $J = 7.6$ and 1.0, CH\textsubscript{ar}), 6.98 (1H, td, $J = 7.8$ and 1.8, CH\textsubscript{ar}), 3.84 (2H, AB pattern, $J_{AB}=17.6$, $\Delta\nu=19.6$ Hz), 3.74 (3H, superimposed s, OCH\textsubscript{3}), 3.74-3.69 (1H, m), 3.20-3.15 (1H, m), 2.98-2.96 (1H, m), 2.26-2.17 (1H, m), 2.07-1.83 (3H, m).

\(^{13}\text{C NMR}\) (100 MHz, CDCl\(_3\)) \(\delta\): 174.3 (CO), 138.8 (CH\(_{ar}\)), 133.0 (CH\(_{ar}\)), 129.4 (CH\(_{ar}\)), 127.9 (CH\(_{ar}\)), 100.8 (C=C), 88.5 (C=C), 87.4 (C=C), 62.7 (CH), 52.6 (CH\(_2\)), 52.2 (OCH\(_3\)), 42.2 (CH\(_2\)), 29.8 (CH\(_2\)), 23.6 (CH\(_2\)).

HRMS (ESI): \(m/z\) calcld for [M+H]\(^+\) C\(_{13}\)H\(_{17}\)N\(_2\): 370.0299, found: 370.0299.

[\(\alpha\)]\(_D\)\(^{25}\) = -93.4 (c= 1.52, CH\(_2\)Cl\(_2\))

2.2. (\(S\))-Methyl 2-(N-(4-(2-iodophenyl)but-3-ynyl)-4-methylphenylsulfonamido)propanoate (10)

\[\text{Ts}(S)\text{CO}_2\text{Me} + \text{CH}_2\text{CH}_2\text{OH} \rightarrow \text{Ts}(S)\text{CO}_2\text{Me} + \text{Ts}(S)\text{CO}_2\text{Me} \]

Synthesis of 9:

To a solution of (\(S\))-methyl 2-(4-methylphenylsulfonamido)propanoate 8 (1.30 g, 5.05 mmol) and PPh\(_3\) (2.65 g, 10.10 mmol) in THF (25 mL) was added, at room temperature, a solution of 3-butyn-1-ol (535 mL, 7.07 mmol) in THF (5 mL). Subsequently a solution of DIAD (2 mL, 10.10 mmol) in THF (10 mL) was added slowly to the above solution. The reaction was monitored by TLC (dichloromethane/Et\(_2\)O: 98/2) and stopped after stirring for 30 min. The solvent was removed in vacuo and the residue was purified by flash chromatography on silica gel (pentane/dichloromethane, 5/5 to 100% dichloromethane) to afford the compound 9 as a liquid (1.04 g, 66%).

\(^1\text{H NMR}\) (400 MHz, CDCl\(_3\)) \(\delta\): 7.69 (2H, d, \(J=\) 8.3, CH\(_{ar}\)), 7.29 (2H, d, \(J=\) 8.0, CH\(_{ar}\)), 4.63 (1H, q, \(J=\) 7.3, CH), 3.51 (3H, s, CH\(_3\)O), 3.45 (1H, ddd, \(J=\) 5.3, 10.3 and 15.3, CH\(_2\)N), 3.30 (1H, ddd, \(J=\) 5.3, 10.3 and 15.3, CH\(_2\)N), 2.70 (1H, dddd, \(J=\) 2.8, 5.3, 10.3 and 15.6, CH\(_2\)C=CH\(_2\)), 2.52 (1H, dddd, \(J=\) 2.8, 5.8, 10.3 and 16.1, CH\(_2\)C=CH\(_2\)), 2.42 (3H, s, CH\(_3\)), 2.00 (1H, t, \(J=\) 2.5, CH=C), 1.43 (3H, d, \(J=\) 7.3, CH\(_3\)).
**Synthesis of 10**

To a solution of o-diodobenzene (596 mg, 1.81 mmol) in a 2:1 mixture of THF:Et₃N (7.5 ml) was added PdCl₂ (6 mg, 0.04 mmol), CuI (2 mg, 0.07 mmol) and PPh₃ (38 mg, 0.14 mmol). This mixture was stirred for 10 min at 40 °C. Then 9 (587 mg, 1.90 mmol) was added to the reaction mixture. The mixture was stirred for 23 h at 40 °C. Then, a 1M HCl solution (20 mL) was added to the reaction mixture and the latter was extracted with AcOEt (3 x 10 mL). After drying over MgSO₄, and concentration in vacuo, crude 10 was purified by flash chromatography on silica gel (pentane/Et₂O, 100/0 to 80/20) to afford pure 10 as a yellow oil (439 mg, 47% (79% with respect to transformed diiodobenzene, 41% of this starting material was recovered)).

**1H NMR** (400 MHz, CDCl₃) δ: 7.82 (1H, dd, J = 0.7 and 8.0, CH₉), 7.73 (2H, d, J = 8.3, CH₉), 7.38 (1H, dd, J = 1.5 and 7.8, CH₉), 7.29 (2H, d, J = 8.0, CH₉), 7.25 (1H, superimposed dt, J = 1.0 and 7.5, CH₉), 6.96 (1H, dt, J = 1.7 and 7.8, CH₉), 4.67 (1H, q, J = 7.3, CH), 3.60 (1H, ddd, J = 5.3, 10.0 and 15.3, CH₂N), 3.53 (3H, s, CH₃O), 3.44 (1H, ddd, J = 6.0, 10.0 and 15.3, CH₂N), 2.97 (1H, ddd, J = 5.3, 10.0 and 15.3, CH₂C≡C), 2.81 (1H, ddd, J = 5.8, 10.0 and 16.0, CH₂C≡C), 2.42 (3H, s, CH₃), 1.49 (3H, d, J = 7.3, CH₃).

**13C NMR** (100 MHz, CDCl₃) δ: 172.0 (CO₂Me), 143.7 (C₉), 138.7 (CH₉), 136.7 (C₉), 132.6 (CH₉), 129.9 (C₉), 129.7 (2xCH₉), 129.2 (CH₉), 127.9 (CH₉), 127.5 (2xCH₉), 101.1 (C₉), 91.0 (C≡C), 84.7 (C≡C), 55.6 (CHN), 52.3 (CH₂O), 44.6 (CH₂N), 22.5 (CH₂), 21.7 (CH₃), 17.1 (CH₃).

**HRMS (ESI):** m/z: calcd for [M+NH₄]⁺ C₂₁H₂₆N₂O₄S: 529.0653, found: 529.0647.
\[\alpha\] = not determined (non measurable because of opacity).

2.3. (R)-3-(4-(2-Iodophenyl)but-3-ynyl)-4-phenyloxazolidin-2-one (R-14)

Synthesis of 13:

To a solution of 11 (2 g, 12.2 mmol) and Cs$_2$CO$_3$ (20 g, 61.2 mmol) in DMF (40 mL) was added homopropargyl alcohol tosylated (12)$^2$ (5.50 g, 24.5 mmol). The reaction mixture was stirred at 60 °C for 4 h, then a first portion of 12 (5.50 g, 2.45 mmol) was added. After stirring for 5 h, a second portion of 10 (2.75 g, 12.2 mmol) was added. The reaction was stirred for an overall 1 day. After addition of a solution of HCl (1M), up to pH = 1, extraction with AcOEt and drying over MgSO$_4$, the solvent was removed in vacuo and the residue was purified by flash chromatography on silica gel (pentane/AcOEt, 90/10 to 80/20). This led to 13 (780 mg, 30%) as an yellow oil.

1H NMR (400 MHz, CDCl$_3$) $\delta$: 7.45-7.37 (3H, m, CH$_{ar}$), 7.32-7.29 (2H, m, CH$_{ar}$), 4.99 (1H, dd, $J$= 7.0 and 8.8, CH), 4.65 (1H, t, $J$= 8.8, CH), 4.13 (1H, dd, $J$= 7.0 and 8.5, CH), 3.62 (1H, dt, $J$= 14.0 and 7.0, CH$_2$N), 2.96 (1H, dt, $J$= 14.0 and 7.0, CH$_2$N); 2.46 (1H, dtd, $J$= 16.8, 7.0 and 2.8, CH$_2$C=CH), 2.31 (1H, dtd, $J$= 16.8, 6.5 and 2.8, CH$_2$C=CH), 2.00 (1H, t, $J$=2.8, CH=CH).

13C NMR (100 MHz, CDCl$_3$) $\delta$: 158.3 (CO), 137.8 (C$_{ar}$), 129.5 (2xCH$_{ar}$), 129.4 (CH$_{ar}$), 127.2 (2xCH$_{ar}$), 81.2 (C=), 70.4 (CH=), 70.1 (CH$_2$O), 60.3 (CHN), 40.8 (NCH$_2$), 17.7 (CH$_2$C=CH).


[α]D²⁵ = -59 (c=0.9, CHCl₃).

Synthesis of R-14

Product (R)-14 was prepared from (R)-13 (780 mg, 3.62 mmol), according to the procedure already described for the synthesis of 10, using diiodobenzene (1.19 g, 3.62 mmol), PdCl₂ (26 mg, 0.14 mmol), CuI (55 mg, 0.29 mmol) and PPh₃ (133 mg, 0.51 mmol) in a 2:1 mixture of THF:Et₃N. The reaction mixture was stirred for 17 h at 40 °C. After work-up, purification by liquid chromatography on silica gel (pentane/CH₂Cl₂, 90/10 to 100% CH₂Cl₂) led to 52 (527 mg, 35% (78% with respect to transformed diiodobenzene, 55% of this starting material was recovered)) as a yellow oil.

1H NMR (400 MHz, CDCl₃) δ: 7.82 (1H, d, J= 7.8, CH₉ar), 7.44-7.35 (4H, m, CH₉ar), 7.33-7.28 (3H, m, CH₉ar), 6.98 (1H, dt, J= 1.5 and 7.8, CH₉ar), 5.11 (1H, dd, J= 6.8 and 8.8, CH), 4.67 (1H, t, J= 8.8, CH), 4.14 (1H, dd, J= 6.8 and 8.5, CH), 3.75 (1H, dt, J= 14.0 and 6.5, CH₂N), 3.07 (1H, dt, J= 17.1 and 6.5, CH₂N), 2.76 (1H, dt, J= 17.1 and 6.8, CH₂C=C), 2.60 (1H, dt, J= 17.1 and 6.5, CH₂C≡C).

13C NMR (100 MHz, CDCl₃) δ: 158.3 (CO), 138.8 (CH₉ar), 137.9(C₉ar), 132.9 (CH₉ar), 129.8 (C₉ar), 129.5 (2xCH₉ar), 129.4 (CH₉ar), 129.3 (CH₉ar); 128.0 (CH₉ar), 127.2 (2xCH₉ar), 100.8 (C₉ar), 90.8 (C≡C), 84.5 (C≡C), 70.2 (CH₂O); 60.2 (CHN), 40.9 (CH₂N), 18.8 (CH₂C≡C).


[α]D²⁵ = -56 (c=0.6, CHCl₃).

(S)-14 was prepared according to the same procedure.
3. General one-pot protocol for the synthesis of enediynes 1a-f

3.1. (S)-Methyl 1-(3-(2-ethynylphenyl)prop-2-ynyl)-5-oxopyrrolidine-2-carboxylate (1a)

Iodide 15\(^1\) (3 g, 7.83 mmol) in THF (75 mL), Et\(_3\)N (15 mL) was added and the reaction mixture was degassed with argon bubbling for 15 min. Then the catalyst, Pd(PPh\(_3\))\(_2\)Cl\(_2\) (110 mg, 2 mol%), and the co-catalyst, CuI (60 mg, 4 mol%), were added to the reaction mixture. After stirring for 10 min trimethylsilyl acetylene (1.66 mL, 11.74 mmol) was added and the reaction mixture was stirred for additional 2 h at room temperature. The conversion of the starting material was monitored by TLC. A solution of TBAF (12 mL of 1 M in THF, 12 mmol) was then added and the reaction mixture stirred further for 30 min. The reaction mixture was then passed through small celite bed, concentrated and the residue was purified by column chromatography on silica gel, using ethyl acetate/pentane (3:7) as eluent, to afford compound 1a (1.72 g, 78% over 2 steps) as a brown liquid.

**\(^1\)H NMR** (400 MHz, CDCl\(_3\)) \(\delta\): 7.48-7.45 (1H, m, CH\(_{ar}\)), 7.40-7.38 (1H, m, CH\(_{ar}\)), 7.29-7.25 (2H, m, CH\(_{ar}\)), 4.89 (1H, d, \(J = \) 17.8, CH\(_2\)N, A part of an AB pattern), 4.65-4.62 (1H, m, CH-CO\(_2\)Me), 4.02 (1H, d, \(J = \) 17.8, CH\(_2\)N, B part of an AB pattern), 3.75 (3H, s, CO\(_2\)CH\(_3\)), 3.31 (1H, s, C≡CH), 2.49-2.36 (3H, m, CH\(_2\)), 2.13-2.10 (1H, m, CH\(_2\)). **\(^13\)C NMR** (100 MHz, CDCl\(_3\)) \(\delta\): 174.5 (CO), 172.2 (CO), 132.6 (CH\(_{ar}\)), 132.1 (CH\(_{ar}\)), 128.6 (CH\(_{ar}\)), 128.3 (CH\(_{ar}\)), 125.4 (C\(_{ar}\)), 124.7 (C\(_{ar}\)), 86.7 (C≡C), 83.3 (C≡C), 82.2 (C≡C), 81.1 (≡CH), 58.4 (CH), 52.6 (OCH\(_3\)), 32.3 (CH\(_2\)N), 29.6 (CH\(_2\)), 22.9 (CH\(_2\)).

**HRMS (ESI):** m/z: calcd for [M+H]\(^+\) C\(_{17}\)H\(_{16}\)NO\(_3\): 282.1125, found: 282.1125.
Chiral HPLC separation of enantiomers: Chiralpak IC, hexane/ethanol 8/2, 1 mL/min, detection UV and CD 254 nm, Rt(S) = 13.41, Rt(R) = 14.78, k(S) = 3.47, k(R) = 3.93, α = 1.13 and Rs = 1.95. ee = 96%.

\[ \alpha^\beta = +12.4 \] (c= 0.78, CH\(_2\)Cl\(_2\)).

3.2. (S)-Methyl-2-(N-(3-(2-ethynylphenyl)prop-2-ynyl)-4-methylphenylsulfonamido) propanoate (1b)

Enediyne 1b was prepared from compound 16\(^1\) (4.00 g, 8.04 mmol), Pd(PPh\(_3\))\(_2\)Cl\(_2\) (113 mg, 2 mol%), CuI (61.3 mg, 4 mol%), trimethylsilyl acetylene (1.7 mL, 12.06 mmol), Et\(_3\)N (20 mL) in THF (100 mL). The reaction mixture was stirred for 2 h. Deprotection was carried out with TBAF solution (1 M in THF) (12.5 mL, 12.5 mmol). The product was purified by column chromatography (20% ethyl acetate/pentane) to yield compound 1b (2.45 g, 77% over 2 steps) as a brown liquid.

\(^{1}\text{H NMR} (400 \text{ MHz, CDCl}_3): 7.83 (2\text{H, d, } J= 8.3, \text{ CH}_ar), 7.48 (1\text{H, m, } \text{CH}_ar), 7.29-7.23 (5\text{H, m, } \text{CH}_ar), 4.71 (1\text{H, q, } J= 7.3, \text{ CHCH}_3), 4.64 (1\text{H, d, } J= 18.8, \text{ CH}_2\text{N, A part of an AB pattern}), 4.41 (1\text{H, d, } J= 18.8, \text{ CH}_2\text{N, B part of an AB pattern}), 3.65 (3\text{H, s, CO}_2\text{CH}_3), 3.24 (1\text{H, s, } \equiv\text{CH}), 2.36 (3\text{H, s, CH}_3), 1.57 (3\text{H, d, } J= 7.3, \text{ CHCH}_3).

\(^{13}\text{C NMR} (100 \text{ MHz, CDCl}_3): 172.0 (\text{CO}), 143.6 (\text{C}_ar), 137.3 (\text{C}_ar), 132.7 (\text{CH}_ar), 132.2 (\text{CH}_ar), 129.6 (2\text{xCH}_ar), 128.5 (\text{CH}_ar), 128.3 (\text{CH}_ar), 127.7 (2\text{xCH}_ar), 125.5 (\text{C}_ar), 124.6 (\text{C}_ar), 88.6 (\text{C}=\text{C}), 83.0 (\text{C}=\text{C}), 82.0 (\text{C}=\text{C}), 81.1 (\equiv\text{CH}), 55.1 (\text{CHCH}_3), 52.4 (\text{OCH}_3), 35.2 (\text{CH}_2\text{N}), 21.6 (\text{CH}_3 \text{ of Ts}), 16.5 (\text{CHCH}_3).

HRMS (ESI): m/z: calcd for [M+H]\(^+\) C\(_{22}\)H\(_{22}\)NO\(_4\)S: 396.1264, found: 396.1264.
Chiral HPLC separation of enantiomers: Chiralcel OD-3, hexane/isopropanol 8/2, 1 mL/min, detection UV and CD 254 nm, Rt(S) = 12.04, Rt(R) = 13.00, k(S) = 3.01, k(R) = 3.33, α = 1.11 and Rs = 1.22. ee = 99%.

[$\alpha$]$_D^{25}$ = -35.8 (c= 0.5, CH$_2$Cl$_2$).

3.3. (S)-3-(3-(2-Ethynylphenyl)prop-2-ynyl)-4-phenyloxazolidin-2-one (S-1c)

Enediyne 1c was prepared from compound 17$^1$ (3.20 g, 7.94 mmol), Pd(PPh$_3$)$_2$Cl$_2$ (111.4 mg, 2 mol%), CuI (60.5 mg, 4 mol%), trimethylsilyl acetylene (1.68 mL, 11.90 mmol), Et$_3$N (16 mL) in THF (80 mL). The reaction mixture was stirred for 12 h. The deprotection was carried out with TBAF solution (1 M in THF) (12 mL, 12 mmol). The product was purified by column chromatography (20% ethyl acetate/pentane) to yield compound 1c (1.57 g, 66% over 2 steps) as a brown liquid.

$^1$H NMR (400 MHz, CDCl$_3$) δ: 7.38-7.36 (1H, m, CH$_{ar}$), 7.29-7.25 (6H, m, CH$_{ar}$), 7.17-7.12 (2H, m, CH$_{ar}$), 5.01 (1H, t, $J$ = 8.3), 4.55 (1H, d, $J$ = 17.8, CH$_2$N, A part of an AB pattern), 4.53 (1H, superimposed t, $J$ = 8.8), 4.05 (1H, t, $J$ = 8.0), 3.51 (1H, d, $J$ = 17.8, CH$_2$N, B part of an AB pattern), 3.15 (1H, s, ≡CH).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ: 157.9 (CO), 136.9 (C$_{ar}$), 132.7 (C$_{ar}$), 132.2 (C$_{ar}$), 129.4 (2xCH$_{ar}$), 129.3 (CH$_{ar}$), 128.7 (CH$_{ar}$), 128.4 (CH$_{ar}$), 127.5 (2xCH$_{ar}$), 125.4 (C$_{ar}$), 124.8 (C$_{ar}$), 86.2 (C=≡C), 83.5 (C≡C), 82.4 (C=≡C), 81.2 (=CH), 70.0 (OCH$_2$), 59.0 (CH), 33.1 (CH$_2$N).

HRMS (ESI): m/z: calcd for [M+H]$^+$ C$_{20}$H$_{16}$NO$_2$: 302.1176, found: 302.1176.

Chiral HPLC separation of enantiomers: Chiralpak IB, hexane/ethanol 9/1, 1 mL/min, detection UV 230 nm and CD 254 nm, Rt(R) = 9.63, Rt(S) = 10.61, k(R) = 2.21, k(S) = 2.54, α = 1.15. ee = 99% for (S) and ee = 99.9% for (R).
[α]D25 = +169.7 (c= 0.67, CH2Cl2) (S-isomer).
[α]D25 = -192.5 (c= 0.49, CH2Cl2) (R-isomer).

3.4. (S)-Methyl 1-(3-(2-ethynylphenyl)prop-2-ynyl)pyrrolidine-2-carboxylate (1d)

Enediyne 1d was prepared from compound 7 (1.80 g, 4.88 mmol), Pd(PPh3)2Cl2 (68.5 mg, 2 mol%), CuI (37 mg, 4 mol%), trimethylsilyl acetylene (1 mL, 7.31 mmol), Et3N (8 mL) in THF (20 mL). The reaction mixture was stirred for 12 h at 60 ºC. The deprotection was carried out with TBAF solution (1 M in THF) (8 mL, 8 mmol). The product was purified by column chromatography (20% ethyl acetate/pentane) to yield compound 1d (978 mg, 75% over 2 steps) as a brown liquid.

\[ \text{1H NMR} \] (400 MHz, CDCl3) δ: 7.49-7.47 (1H, m, CHar), 7.43-7.41 (1H, m, CHar), 7.29-7.22 (2H, m, CHar), 3.88 (2H, AB pattern, JAB = 17.6, Δν = 22.3 Hz), 3.73 (3H, s, OCH3), 3.67 (1H, dd, J = 6.5 and 9.0), 3.27 (1H, s, =CH), 3.12-3.08 (1H, m), 2.94-2.88 (1H, m), 2.22-2.13 (1H, m), 2.04-1.79 (3H, m). \[ \text{13C NMR} \] (100 MHz, CDCl3) δ: 174.3 (CO), 132.7 (CHar), 132.1 (CHar), 128.6 (CHar), 127.9 (CHar), 126.3 (Cm), 124.7 (Cm), 88.6 (C=C), 84.0 (C=C), 82.6 (C=C), 81.0 (CH≡), 62.5 (CH), 52.4 (CH2), 52.1 (OCH3), 42.2 (CH2), 29.8 (CH2), 23.5 (CH2).


Chiral HPLC separation of enantiomers: Chiralpak ID, hexane/isopropanol 95/5, 1 mL/min, detection UV and CD 254 nm, Rt (S) = 7.27 Rt (R) = 7.97 and k(S) = 1.42, k(R) = 1.66, α = 1.17 and Rs = 2.49. ee = 99%.

[α]D25 = -106.5 (c= 0.81, CH2Cl2)
3.5. (S)-Methyl-2-(N-(3-(2-ethynylphenyl)prop-2-ynyl)-4-methylphenylsulfonamido)propanoate (1e)

(i) TMS, Pd(PPh₃)₂Cl₂, CuI, Et₃N, THF, rt, 2 h
(ii) TBAF solution in THF, 30 min

Enediyne 1e was prepared from compound 10 (1.00 g, 1.96 mmol), Pd(PPh₃)₂Cl₂ (28 mg, 2 mol%), CuI (15 mg, 4 mol%), trimethylsilyl acetylene (0.41 mL, 2.93 mmol), Et₃N (4 mL) in THF (10 mL). The reaction mixture was stirred for 2 h in room temperature. Deprotection was carried out with TBAF solution (1 M in THF) (3.0 mL, 3.00 mmol). The product was purified by column chromatography (20% ethyl acetate/pentane) to yield compound 1e (700 mg, 87.5%) as a yellowish liquid.

**¹H NMR** (400 MHz, CDCl₃) δ: 7.72 (2H, d, J= 8.3, CH₉), 7.47 (1H, dd, J= 1.8 and 7.0, CH₉), 7.38 (1H, dd, J= 1.5 and 7.3, CH₉), 7.28 (2H, superimposed d, J= 8.3, CH₉), 7.27-7.21 (2H, superimposed m, CH₉), 4.66 (1H, q, J= 7.3, CHN), 3.58 (1H, ddd, J= 5.0, 9.8 and 15.8), 3.52 (3H, s, CH₃O), 3.42 (1H, ddd, J= 6.0, 9.8 and 15.8), 3.27 (1H, s, ≡CH), 2.95 (1H, ddd, J= 5.2, 9.8 and 16.8), 2.81 (1H, ddd, J= 6.0, 10.0 and 16.8), 2.41 (3H, s, CH₃), 1.48 (3H, d, J= 7.3, CH₃).

**¹³C NMR** (100 MHz, CDCl₃) δ: 172.0 (CO₂Me), 143.7 (C₉), 136.8 (C₉), 132.7 (CH₉), 132.0 (CH₉), 129.7 (2xCH₉), 128.6 (CH₉), 127.7 (CH₉), 127.5 (2xCH₉), 126.5 (C₉), 124.6 (C₉), 91.3 (C=CC), 82.4 (C=C), 81.0 (C=CC), 80.9 (=CH), 55.6 (CHN), 52.3 (CH₃O), 44.8 (CH₂N), 22.5 (CH₂), 21.7 (CH₃), 17.1 (CH₃).

**HRMS (ESI):** m/z: calc'd for [M+H]⁺ C₂₃H₂₄NO₄S: 410.1421, found: 410.1426.

**Chiral HPLC** separation of enantiomers: Chiralpak IC, hexane/ethanol 7/3, 1 mL/min, detection UV and CD 254 nm, Rt (S) = 7.15, Rt (R) = 8.05 and k(S) = 1.38, k(R) = 1.68, α = 1.22 and Rs = 2.34. ee = 83%.

[α]D<sub>25</sub> = -24.2 (c= 0.64, CH₂Cl₂)
3.6. (R)-3-(4-(2-ethynylphenyl)but-3-ynyl)-4-phenyloxazolidin-2-one ((R)-1f)

Enediyne 1f was prepared from compound 14 (280 mg, 0.67 mmol), Pd(PPh₃)₂Cl₂ (10 mg, 2 mol%), CuI (5 mg, 4 mol%), trimethylsilyl acetylene (0.19 mL, 1.34 mmol), Et₃N (2 mL) in THF (5 mL). The reaction mixture was stirred for 2 h in room temperature. Deprotection was carried out with TBAF solution (1 M in THF) (1.5 mL, 1.5 mmol). The product was purified by column chromatography (20% ethyl acetate/pentane) to yield compound 1f (179 mg, 85%) as a yellowish liquid.

\[ ^1H\text{ NMR} \quad (400 \text{ MHz, CDCl}_3) \delta: 7.48 \text{ (1H, dd, } J = 2.0 \text{ and } 7.0, \text{ CH}_\text{ar}), 7.42-7.37 \text{ (4H, m, CH}_\text{ar}), 7.32-7.23 \text{ (4H, m, CH}_\text{ar}), 5.12 \text{ (1H, dd, } J = 6.8 \text{ and } 8.8, \text{ CH}), 4.65 \text{ (1H, t, } J = 8.8, \text{ CH}), 4.13 \text{ (1H, dd, } J = 6.8 \text{ and } 8.5, \text{ CH}), 3.73 \text{ (1H, dt, } J = 14.0 \text{ and } 6.5, \text{ CH}_2\text{N}), 3.27 \text{ (1H, s, } =\text{CH }), 3.05 \text{ (1H, dt, } J = 13.8 \text{ and } 6.5, \text{ CH}_2\text{N}), 2.76 \text{ (1H, dt, } J = 17.0 \text{ and } 7.0, \text{ CH}_2\text{C=C}), 2.60 \text{ (1H, dt, } J = 17.0 \text{ and } 6.3, \text{ CH}_2\text{C=C}).
\]

\[ ^13\text{C NMR} \quad (100 \text{ MHz, CDCl}_3) \delta: 158.3 \text{ (CO), 138.0 (C}_\text{ar}), 132.8 \text{ (CH}_\text{ar}), 132.2 \text{ (CH}_\text{ar}), 129.5 \text{ (2C}_\text{H}_\text{ar}), 129.3 \text{ (CH}_\text{ar}), 128.7 \text{ (CH}_\text{ar}), 129.3 \text{ (CH}_\text{ar}); 127.9 \text{ (CH}_\text{ar}), 127.3 \text{ (2C}_\text{H}_\text{ar}), 126.3 \text{ (C}_\text{ar}), 124.5 \text{ (C}_\text{ar}), 91.1 \text{ (C=C), 82.4 (C=C), 80.9 (C=C), 80.8 (C=C), 70.1 (CH}_2\text{O); 60.3 (CHN), 40.9 (CH}_2\text{N), 18.8 (CH}_2\text{C=C}).
\]

HRMS (ESI): m/z: calcd for [M+H]^+ C_{21}H_{17}NO_2: 315.3652, found: 316.1332.

Chiral HPLC separation of R-enantiomers: Chiralpak IC, hexane/ethanol 9/1, 1 mL/min, detection UV and CD 254 nm, Rt (S) = 14.73 Rt (R) = 13.07 and k(R) = 3.36, k(S) = 3.91, α = 1.16 and Rs = 3.52. ee = 99.9%.

\[ [\alpha]_D^{25} = -64.1 \text{ (c= 0.44, CH}_2\text{Cl}_2) \]
Chiral HPLC separation of S-enantiomers: Chiralpak IC, hexane/ethanol 9/1, 1 mL/min, detection UV and CD 254 nm, Rt (S) = 14.73 Rt (R) = 13.07 and k(S) = 1.42, k(R) = 1.66, α = 1.17 and Rs = 4.24. ee = 99.9%.

\[\alpha_d^{25} = +59.4 \text{ (c= 0.87, CH}_2\text{Cl}_2)\]

4. General One-Pot Crabbé Homologation-Radical Cascade Cyclization

4.1. Cyclization of (S)-1a

\[
\text{(CH}_2\text{O)}_n (2.5 \text{ equiv.}) \quad \text{Cy}_2\text{NH (1.8 equiv.)} \\
\text{Cu}I (0.5 \text{ equiv.}) \quad \text{1,4-dioxane, reflux, 2 h}
\]

\[
\text{(S)-1a} \quad \text{ee = 96%}
\]

\[
\text{(R)-2a (81%)} \quad \text{ee = 95%}
\]

(CH$_2$O)$_n$ (27 mg, 0.89 mmol), CuI (34 mg, 0.18 mmol), 1,4-dioxane (1 mL), enediyne (S)-1a (100 mg, 0.36 mmol) and dicyclohexylamine (0.13 mL, 0.64 mmol) were added sequentially into an oven-dried reaction tube equipped with a reflux condenser under an argon atmosphere. The resulting mixture was stirred at reflux for 2 h. Solvent was evaporated under vacuo and redissolved in DCM, filtered, and the filtrate was concentrated and purified by column chromatography on silica gel using 1:1 ethyl acetate:pentane as eluent to afford the cyclized product (R)-2a (85 mg, 81%, ee = 95%).

(R)-Methyl 3-oxo-1,2,3,5,12,12a-hexahydrobenzo[g]pyrrolo [1,2-b]isoquinoline-12a-carboxylate (R-2a):

White solid, mp= 205.9 °C (acetonitrile); $^1$H NMR (400 MHz, CDCl$_3$) δ: 7.78-7.73 (2H, m, CH$_{ar}$), 7.64 (1H, s, CH$_{ar}$), 7.63 (1H, s, CH$_{ar}$), 7.46-7.41 (2H, m, CH$_{ar}$), 5.09 (1H, d, J = 17.3, CH$_2$N, A part of an AB pattern), 4.63 (1H, d, J = 17.3, CH$_2$N, B part of an AB pattern), 3.74 (1H, d, J = 15.3, CCH$_2$, A part of an AB pattern), 3.57 (3H, s, OCH$_3$), 3.08 (1H, d, J = 15.3, CCH$_2$, B part of an AB pattern), 2.64-2.47 (3H, m), 2.26-2.17 (1H, m).
\(^{13}\text{C NMR}\) (100 MHz, CDCl\(_3\)) \(\delta\): 174.6 (CO), 173.4 (CO), 132.7 (C\(_\text{ar}\)), 132.4 (C\(_\text{ar}\)), 129.7 (C\(_\text{ar}\)), 129.3 (C\(_\text{ar}\)), 127.6 (CH\(_\text{ar}\)), 127.5 (CH\(_\text{ar}\)), 127.4 (CH\(_\text{ar}\)), 126.2 (CH\(_\text{ar}\)), 126.1 (CH\(_\text{ar}\)), 125.5 (CH\(_\text{ar}\)), 65.7 (C), 52.9 (OCH\(_3\)), 42.6 (CH\(_2\)), 40.0 (CH\(_2\)), 31.4 (CH\(_2\)), 29.7 (CH\(_2\)).

**HRMS** (ESI): m/z: calcd for [M+H]+ \(\text{C}_{18}\text{H}_{18}\text{NO}_3\): 296.1281, found: 296.1282.

**Chiral HPLC** separation of enantiomers: Chiralpak IB, hexane/ethanol 7/3, 1 mL/min, detection UV 230 nm and CD 254 nm, Rt (S) = 8.15 Rt (R) = 7.02 and \(k(S) = 1.72, k(R) = 1.34, \alpha = 1.28\) and \(Rs = 2.8\). \(\text{ee} = 95\%\) (\(\text{ee} = 99.9\%\) after recrystallization).

\([\alpha]_D^{25} = -139.6 \ (c= 0.49, \text{CH}_2\text{Cl}_2)\)

**X-ray structure of (R)-2a**

### 4.2. Cyclization of (S)-1b

Enediyne (S)-1b (100 mg, 0.25 mmol) was allowed to react with (CH\(_2\)O)\(_n\) (19 mg, 0.63 mmol), CuI (24 mg, 0.13 mmol) and dicyclohexylamine (0.10 mL, 0.46 mmol) in refluxing 1,4-dioxane (1 mL) for 2 h. The products were purified by column chromatography on silica gel using 1:9 ethyl acetate:pentane as eluent to afford (R)-2b (64 mg, 62%, \(\text{ee} = 85\%\)) and olefin 3b (4.1 mg, 4%).
(R)-Methyl 3-methyl-2-tosyl-1,2,3,4-tetrahydrobenzo[g]isoquinoline-3-carboxylate (R-2b):

Colorless oil. $^1$H NMR (400 MHz, CDCl$_3$) δ: 7.81-7.78 (2H, m, CH$_2$ar), 7.75 (2H, d, $J$ = 8.3, CH$_2$ar), 7.63 (1H, s, CH$_2$ar), 7.54 (1H, s, CH$_2$ar), 7.48-7.46 (2H, m, CH$_2$ar), 7.23 (2H, d, $J$ = 8.3, CH$_2$ar), 4.55 (2H, s, CH$_2$), 3.82 (3H, s, OCH$_3$), 3.42 (1H, d, $J$ = 14.6, CH$_2$, A part of an AB pattern), 3.02 (1H, d, $J$ = 14.8, CH$_2$, B part of an AB pattern), 2.38 (3H, s, CH$_3$), 1.56 (3H, s, CH$_3$).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ: 174.8 (CO), 143.4 (C$_{ar}$), 138.3 (C$_{ar}$), 133.2 (C$_{ar}$), 132.6 (C$_{ar}$), 132.5 (C$_{ar}$), 131.4 (C$_{ar}$), 129.7 (2xCH$_{ar}$), 127.8 (CH$_{ar}$), 127.6 (CH$_{ar}$), 127.3 (2xCH$_{ar}$), 126.4 (CH$_{ar}$), 126.3 (CH$_{ar}$), 126.1 (CH$_{ar}$), 124.3 (CH$_{ar}$), 63.6 (C), 52.9 (OCH$_3$), 47.0 (CH$_2$), 42.1 (CH$_2$), 24.3 (CH$_3$), 21.6 (CH$_3$).

HRMS (ESI): m/z: calcd for [M+H]$^+$ C$_{23}$H$_{24}$NO$_4$S: 410.1421, found: 410.1420.

Chiral HPLC separation of enantiomers: Chiralpak IA, hexane/ethanol 7/3, 1 mL/min, detection UV 230 nm and CD 254 nm, Rt (S) = 12.07 Rt (R) = 8.67 and $k(S)$ = 3.02, $k(R)$ = 1.89, $\alpha$ = 1.60 and Rs = 6.77. ee = 85%.

[$\alpha$]$_D^{25}$ = +11.6 (c= 0.50, CH$_2$Cl$_2$)

Methyl 2-(4-methyl-N-((3-methylnaphthalen-2-yl)methyl)phenylsulfonamido)acrylate (3b):

Colourless oil. $^1$H NMR (400 MHz, CDCl$_3$) δ: 7.75 (2H, d, $J$ = 8.3, CH$_2$ar), 7.70 (1H, d, $J$ = 8.0, CH$_2$ar), 7.65 (1H, d, $J$ = 7.8, CH$_2$ar), 7.57 (1H, s, CH$_2$ar), 7.48 (1H, s, CH$_2$ar), 7.42-7.35 (2H, m, CH$_2$ar), 7.32 (2H, d, $J$ = 8.0, CH$_2$ar), 6.15 (1H, s, -CH$_2$H$_2$), 5.66 (1H, s, =CH$_2$H$_2$), 4.79 (2H, s, CH$_2$N), 3.56 (3H, s, OCH$_3$), 2.54 (3H, s, CH$_3$), 2.45 (3H, s, CH$_3$).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ: 164.2 (CO), 143.9 (C), 135.7 (C$_{ar}$), 135.5 (C$_{ar}$), 135.4 (C$_{ar}$), 133.5 (C$_{ar}$), 131.8 (C$_{ar}$), 131.6 (C$_{ar}$), 129.8 (CH$_{ar}$), 129.6 (2xCH$_{ar}$), 128.8 (CH$_{ar}$), 128.5 (=CH$_2$), 128.1 (2xCH$_{ar}$), 127.6 (CH$_{ar}$), 127.0 (CH$_{ar}$), 126.4 (CH$_{ar}$), 125.4 (CH$_{ar}$), 52.3 (OCH$_3$), 51.4 (CH$_2$N), 21.8 (CH$_3$), 19.6 (CH$_3$).

4.3. Cyclization of (S)-1c

Enediyne (S)-1c (100 mg, 0.33 mmol) was allowed to react with (CH$_2$O)$_n$ (25 mg, 0.83 mmol), CuI (32 mg, 0.17 mmol) and dicyclohexylamine (0.12 mL, 0.60 mmol) in refluxing 1,4-dioxane (1 mL) for 2 h. The products were purified by column chromatography on silica gel using 3:7 ethyl acetate:pentane as eluent to afford (S)-2c (73 mg, 70%, ee= 87%).

(S)-12a-phenyl-12,12a-dihydro-1H-benzo[g]oxazolo [3,4-b]isoquinolin-3(5H)-one (S)-2c:

White solid, mp= 243.3 °C (EtOAc); $^1$H NMR (400 MHz, CDCl$_3$) δ: 7.75-7.73 (1H, m, CH$_{ar}$), 7.67 (1H, d, J= 7.3, CH$_{ar}$), 7.67 (1H, superimposed s, CH$_{ar}$), 7.49 (1H, s, CH$_{ar}$), 7.43-7.37 (4H, m, CH$_{ar}$), 7.33-7.28 (2H, m, CH$_{ar}$), 7.20 (1H, tt, J= 7.3 and 1.3, CH$_{ar}$), 5.17 (1H, d, J= 17.3, CH$_2$N, A part of an AB pattern), 4.45 (1H, d, J= 8.5, CH$_2$O, A part of an AB pattern), 4.42 (1H, d, J= 16.8, CH$_2$N, B part of an AB pattern), 4.31 (1H, d, J= 8.5, CH$_2$O, B part of an AB pattern), 3.79 (1H, d, J= 15.6, CH$_2$C, A part of an AB pattern), 3.51 (1H, d, J= 15.6, CH$_2$C, B part of an AB pattern).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ: 158.0 (CO), 139.1 (C$_{ar}$), 132.5 (C$_{ar}$), 132.4 (C$_{ar}$), 130.2 (C$_{ar}$), 129.5 (2xCH$_{ar}$), 129.2 (C$_{ar}$), 128.3 (CH$_{ar}$), 127.8 (CH$_{ar}$), 127.4 (CH$_{ar}$), 127.3 (CH$_{ar}$), 126.2 (2xCH$_{ar}$), 126.1 (CH$_{ar}$), 126.0 (CH$_{ar}$), 125.0 (CH$_{ar}$), 76.5 (OCH$_2$), 62.2 (C), 42.4 (CH$_2$), 37.1 (CH$_2$).

HRMS (ESI): m/z: calcd for [M+H]$^+$ C$_{21}$H$_{18}$NO$_2$: 316.1332, found: 316.1332.
**Chiral HPLC** separation of enantiomers: Chiralpak IC, hexane/ethanol 7/3, 1 mL/min, detection UV 230 nm and CD 254 nm, Rt (S) = 15.26 Rt (R) = 17.37 and k(S) = 4.09, k(R) = 4.79, \( \alpha = 1.17 \) and Rs = 2.60. ee = 87%.

\([\alpha]_D^{25} = +331.1 \text{ (c= 0.45, CH}_2\text{Cl}_2)\]

**4.4. Cyclization of (R)-1c**

![Chemical structure diagram]

Enediyne (R)-1c (100 mg, 0.33 mmol) was allowed to react with \((\text{CH}_2\text{O})_n\) (25 mg, 0.83 mmol), CuI (32 mg, 0.17 mmol) and dicyclohexylamine (0.12 mL, 0.60 mmol) in refluxing 1,4-dioxane (1 mL) for 2 h. The products were purified by column chromatography on silica gel using 3:7 ethyl acetate:pentane as eluent to afford (R)-2c (73 mg, 70%, ee= 90%) as white solid, mp= 231.3 °C (EtOAc).

**HRMS (ESI):** m/z: calcd for [M+H]^+ \text{C}_21\text{H}_{18}\text{NO}_2: 316.1332, found: 316.1332.

**Chiral HPLC** separation of enantiomers: Chiralpak IC, hexane/ethanol 7/3, 1 mL/min, detection UV 230 nm and CD 254 nm, Rt (S) = 15.26 Rt (R) = 17.37 and k(S) = 4.09, k(R) = 4.79, \( \alpha = 1.17 \) and Rs = 2.60. ee = 90%.

\([\alpha]_D^{25} = -316.8 \text{ (c= 0.63, CH}_2\text{Cl}_2)\]
4.5 Cyclization of (S)-1d

Enediyne (S)-1d (100 mg, 0.37 mmol) was allowed to react with (CH₂O)ₙ (28 mg, 0.94 mmol), CuI (36 mg, 0.19 mmol) and dicyclohexylamine (0.13 mL, 0.67 mmol) in refluxing 1,4-dioxane (1 mL) for 2 h. The products were purified by column chromatography on silica gel using 2:8 ethyl acetate:pentane as eluent to afford (R)-2d (70 mg, 67%, ee= 97%) as white solid, mp= 116.3 °C (precipitated from ethyl acetate:pentane).

(R)-Methyl 1,2,3,5,12,12a-hexahydrobenzo[g]pyrrolo[1,2-b]isoquinolin-12a-carboxylate (R-2d):

\[
\begin{align*}
\text{C}_{18} \text{H}_{19} \text{NO}_2 & \quad \text{Mol. Wt.: 281.3490} \\
\text{HRMS (ESI): m/z: calcd for [M+H]^+ C}_{18}\text{H}_{20}\text{NO}_2: 282.1489, found: 282.1490.}
\end{align*}
\]
Chiral HPLC separation of enantiomers: Chiralpak AD-H, hexane/ethanol 95/5, 1 mL/min, detection UV 230 nm and CD 254 nm, Rt (S) = 8.96 Rt (R) = 11.13 and k(S) = 1.99, k(R) = 2.71, \( \alpha = 1.36 \) and Rs = 3.96. ee = 97%.

\[ [\alpha]_D^{25} = +67.5 \quad (c= 0.40, \text{CH}_2\text{Cl}_2) \]

4.6. Cyclization of (S)-1e

Enediyne (S)-1e (100 mg, 0.24 mmol) was allowed to react with (CH_2O)_n (18.3 mg, 0.61 mmol), CuI (23.3 mg, 0.12 mmol) and dicyclohexylamine (0.10 mL, 0.44 mmol) in refluxing 1,4-dioxane (1 mL) for 2 h. The products were purified by column chromatography on silica gel using 1:9 ethyl acetate:pentane as eluent to afford (R)-2e (45 mg, 44%, ee= 56%) and olefin 3e (20 mg, 19%).

(R)-Methyl 2-methyl-3-tosyl-2,3,4,5-tetrahydro-1H-naphtho[2,3-d]azepine-2-carboxylate (R-2e):

Colorless oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \): 7.80 (2H, d, \( J=8.2, \text{CH}_\text{ar})\), 7.76-7.72 (2H, m, CH\(_\text{ar}\)), 7.51 (1H, s, CH\(_\text{ar}\)), 7.50 (1H, s, CH\(_\text{ar}\)), 7.45-7.42 (2H, m, CH\(_\text{ar}\)), 7.24 (2H, d, \( J=8.3, \text{CH}_\text{ar}\)), 3.81-3.74 (1H, m), 3.77 (3H, superimposed s, OCH\(_3\)), 3.67-3.52 (1H, m), 3.63 (1H, superimposed d, \( J=15.6, \text{A part of an AB pattern} \)), 3.24-3.04 (2H, m), 3.14 (1H, superimposed d, \( J=15.0, \text{B part of an AB pattern} \)), 2.40 (3H, s, CH\(_3\)), 1.54 (3H, s, CH\(_3\)).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \): 174.4 (CO), 143.6 (C\(_\text{ar}\)), 137.9 (C\(_\text{ar}\)), 136.6 (C\(_\text{ar}\)), 133.3 (C\(_\text{ar}\)), 133.0 (C\(_\text{ar}\)), 132.3 (C\(_\text{ar}\)), 129.8 (CH\(_\text{ar}\)), 129.6 (2xCH\(_\text{ar}\)), 127.9 (2xCH\(_\text{ar}\)), 127.6
(CH$_2$), 127.4 (CH$_2$), 127.1 (CH$_2$), 126.2 (CH$_2$), 125.9 (CH$_2$), 66.3 (C), 52.7 (OCH$_3$),
45.9 (CH$_2$), 44.2 (CH$_2$), 35.2 (CH$_2$), 22.1 (CH$_3$), 21.7 (CH$_3$).

**HRMS (ESI):** m/z: calcld for [M+H]$^+$ C$_{24}$H$_{26}$NO$_4$S: 424.1577, found: 424.1573.

**Chiral HPLC** separation of enantiomers: Chiralpak IB, hexane/ethanol 9/1, 1 mL/min,
detection UV 230 nm and CD 254 nm, Rt (S) = 11.61 Rt (R) = 12.94 and k(S) = 2.87,
k(R) = 3.31, $\alpha = 1.15$ and Rs = 2.19. ee = 56%.

[$\alpha$]$_{D}^{25}$ = -10.4 (c= 0.48, CH$_2$Cl$_2$)

Methyl 2-(4-methyl-N-(2-(3-methylnaphthalen-2-yl)ethyl)phenylsulfonamido)acrylate (3e):

Colourless oil; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 7.72-7.69 (2H, m, CH$_{ar}$), 7.66 (2H, d, $J= 8.3$, CH$_{ar}$), 7.57 (1H, s, CH$_{ar}$), 7.52 (1H, s, CH$_{ar}$),
7.40-7.38 (2H, m, CH$_{ar}$), 7.21 (2H, d, $J= 8.3$, CH$_{ar}$), 6.45 (1H, s, =CH$_A$H$_B$), 5.81 (1H, s, =CH$_A$H$_B$), 3.67 (3H, s, OCH$_3$), 3.64-3.60 (2H, m, CH$_2$N), 3.03-2.99 (2H, m, CH$_2$), 2.42 (3H, s, CH$_3$), 2.39 (3H, s, CH$_3$).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 164.4 (CO), 143.7 (C), 136.2 (C$_{ar}$), 136.1 (C$_{ar}$), 135.1 (C$_{ar}$), 134.7 (C$_{ar}$), 132.8 (C$_{ar}$), 132.3 (C$_{ar}$), 129.5 (2xCH$_{ar}$), 128.5 (=CH$_2$), 128.4 (CH$_{ar}$),
128.1 (CH$_{ar}$), 127.8 (2xCH$_{ar}$), 127.2 (CH$_{ar}$), 127.0 (CH$_{ar}$), 125.7 (CH$_{ar}$), 125.4 (CH$_{ar}$),
52.6 (OCH$_3$), 49.7 (CH$_2$N), 33.1 (CH$_2$), 21.7 (CH$_3$), 19.8 (CH$_3$).

**HRMS (ESI):** m/z: calcld for [M+H]$^+$ C$_{24}$H$_{26}$NO$_4$S: 424.1577, found: 424.1576.

4.7. Cyclization of (S)-1f

Enediyne (S)-1f (100 mg, 0.32 mmol) was allowed to react with (CH$_2$O)$_n$ (24 mg, 0.79 mmol), Cul (30 mg, 0.16 mmol) and dicyclohexylamine (0.11 mL, 0.57 mmol) in
refluxing 1,4-dioxane (1 mL) for 2 h. The products were purified by column chromatography on silica gel using 2:8 ethyl acetate:pentane as eluent to afford (S)-2f (40 mg, 38.5%, ee= 81%) and olefin 3f (25 mg, 24%).

(S)-13a-phenyl-5,6,13,13a-tetrahydronaphtho[2,3-d]oxazolo[3,4-a]azepin-3(1H)-one (S-2f):

Yellowish oil, \[^1\text{H}\text{ NMR}\] (400 MHz, CDCl\(_3\)) \(\delta\): 7.77-7.75 (1H, m, CH\(_{\text{ar}}\)), 7.72-7.70 (1H, m, CH\(_{\text{ar}}\)), 7.68 (1H, s, CH\(_{\text{ar}}\)), 7.54 (1H, s, CH\(_{\text{ar}}\)), 7.43-7.41 (2H, m, CH\(_{\text{ar}}\)), 7.34-7.33 (4H, m, CH\(_{\text{ar}}\)), 7.22-7.20 (1H, m, CH\(_{\text{ar}}\)), 4.35 (1H, d, J = 8.3, A part of an AB pattern), 4.29-4.26 (1H, m), 4.11 (1H, d, J = 8.3, B part of an AB pattern), 3.74 (1H, d, J = 14.6, A part of an AB pattern), 3.63 (1H, d, J = 14.0, B part of an AB pattern), 3.21-3.18 (2H, m), 3.03-2.99 (1H, m).

\[^{13}\text{C}\text{ NMR}\] (100 MHz, CDCl\(_3\)) \(\delta\): 158.2 (CO), 133.7 (C\(_{\text{ar}}\)), 133.0 (C\(_{\text{ar}}\)), 132.6 (C\(_{\text{ar}}\)), 129.4 (2xCH\(_{\text{ar}}\)), 128.2 (CH\(_{\text{ar}}\)), 128.0 (CH\(_{\text{ar}}\)), 127.3 (2xCH\(_{\text{ar}}\)), 127.2 (CH\(_{\text{ar}}\)), 126.2 (CH\(_{\text{ar}}\)), 126.0 (CH\(_{\text{ar}}\)), 125.9 (2xCH\(_{\text{ar}}\)), 76.0 (OCH\(_2\)), 65.3 (C), 44.4 (CH\(_2\)N), 40.9 (CH\(_2\)), 33.6 (CH\(_2\)).

Due to unexplained low intensity (slow relaxation time) of aliphatic carbons, the spectra was assigned from 2D HSQC sequence which allowed unambiguous measurement of chemical shifts.

HRMS (ESI): m/z: calcd for [M+H]\(^+\) \(\text{C}_{22}\text{H}_{19}\text{NO}_2\): 330.1489, found: 330.1488.

Chiral HPLC separation of enantiomers: Chiralpak IA, hexane/ethanol 7/3, 1 mL/min, detection UV 230 nm and CD 254 nm, Rt (S) = 10.61 Rt (R) = 12.85 and k(S) = 2.54, k(R) = 3.28, \(\alpha = 1.30\) and Rs = 4.17. ee = 81%.

\([\alpha]_D^{25}\) = +98.4 (c = 0.94, CH\(_2\)Cl\(_2\))

3-(2-(3-Methylnaphthalen-2-y1)ethyl-4-phenyloxazol-2(3H)-one (3f):

White solid, mp= 97.8 °C (precipitated from ethyl acetate:pentane), \[^1\text{H}\text{ NMR}\] (400 MHz, CDCl\(_3\)) \(\delta\): 7.69-7.64 (2H, m, CH\(_{\text{ar}}\)), 7.47 (1H, s, CH\(_{\text{ar}}\)), 7.41-7.38 (3H, m, CH\(_{\text{ar}}\)), 7.38 (1H, superimposed s, CH\(_{\text{ar}}\)), 7.31 (2H, t, J = 7.3, CH\(_{\text{ar}}\)), 7.02 (2H, d, J = 7.0, CH\(_{\text{ar}}\)), 6.72 (1H, s, CH=), 3.89 (2H, t, J = 7.3, CH\(_2\)N), 3.01
(2H, t, J= 7.3, CH₂), 2.17 (3H, s, CH₃).

¹³C NMR (100 MHz, CDCl₃) δ: 156.2 (CO), 134.6 (C₆), 134.5 (C₆), 132.9 (C₆), 132.4 (C₆), 129.9 (C₆), 129.6 (CH₆), 129.0 (2xCH₆), 128.7 (2xCH₆), 128.5 (CH₆), 128.4 (CH₆), 127.2 (CH₆), 126.9 (CH₆), 126.4 (C=), 125.8 (CH₆), 125.4 (CH₆), 123.9 (CH=), 42.5 (CH₂), 32.3 (CH₂), 19.4 (CH₃).


4.8. Cyclization of (R)-1f

Enediyne (R)-1f (100 mg, 0.32 mmol) was allowed to react with (CH₂O)ₙ (24 mg, 0.79 mmol), CuI (30 mg, 0.16 mmol) and dicyclohexylamine (0.11 mL, 0.57 mmol) in refluxing 1,4-dioxane (1 mL) for 2 h. The products were purified by column chromatography on silica gel using 2:8 ethyl acetate:pentane as eluent to afford (R)-2f (40 mg, 38.5%, ee= 79%) as yellowish oil and olefin 3f (25 mg, 24%).


Chiral HPLC separation of enantiomers: Chiralpak IA, hexane/ethanol 7/3, 1 mL/min, detection UV 230 nm and CD 254 nm. Rt (S) = 10.61 Rt (R) = 12.85 and k(S) = 2.54, k(R) = 3.28, α = 1.30 and Rs = 4.17. ee = 79%.

[α]D²⁵ = -112.0 (c= 0.44, CH₂Cl₂).
5. HPLC spectra

Method description: Chiralpak IC, Hexane:Ethanol 80:20, 1 ml/min, DAD and CD 254nm
Method description: Chiralpak IB, Hexane/Ethanol 70:30, 1 ml/min, DAD and CD 254 nm

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Electronic Supplementary Material (ESI) for Chemical Communications
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Method description: Chiralpak IA, Hexane/Ethanol 70:30, 1 ml/min, DAD and CD 254nm

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Method description: Chiralpak IA, Hexane/Ethanol 70:30, 1 ml/min, DAD and CD 229nm

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6. NMR spectra
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HNMR in CD$_3$CN

(S)-2f

CD$_3$CN
HNMR in CDCl₃