Supporting Information

Ynamide Carbopalladation: A Flexible Route to Mono-, Bi- and Tricyclic Azacycles

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SUPPORTING INFORMATION

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1. General experimental considerations

**NMR Spectra:** $^1$H NMR spectra were recorded using an internal deuterium lock for the residual protons in CDCl$_3$ ($\delta$ 7.26) at ambient probe temperatures on the following instruments: Bruker AV400 (400 MHz), Bruker AMX 500 (500 MHz), Bruker DPX200 (200 MHz) or Bruker DPX250 (250 MHz). Data are presented as follows: chemical shift, peak multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, sex = sextet, m = multiplet, br = broad, app = apparent), coupling constants and interpretations. Chemical shifts are expressed in ppm on a $\delta$ scale relative to SiMe$_4$ ($\delta$ = 0 ppm) and coupling constants ($J$) are given in Hz. Assignments were made either on the basis of unambiguous chemical shift or coupling patterns, or by analogy to fully interpreted spectra for structurally related compounds. $^{13}$C NMR spectra were recorded using an internal deuterium lock using solvents CDCl$_3$ ($\delta$ 77.0) at ambient probe temperatures on the following instruments: Bruker AV400 (100 MHz) or Bruker AMX 500 (125 MHz).

**Infra-red spectra:** Recorded on Perkin Elmer Paragon 1000 spectrometer with the sample prepared as a thin film between NaCl plates, or using a PIKE-Miracle Diamond /ZnSe ATR module.

**Mass spectra:** Accurate mass (HRMS) data was acquired using electrospray ionisation on a Bruker MicroTOF (resolution = 5000 FWHM) using tetraoctylammonium bromide as a lock-mass in both positive and negative ion modes, or via CI or FI on a Micromass GCT (resolution = 7000 FWHM) using isoamyl acetate as a lock-mass. High resolution values are calculated to 4 decimal places from the molecular formula, and all values are within a tolerance of 5 ppm.

**Melting points:** Obtained using a Reichert-Koffler block and are uncorrected.

**Optical rotations:** Performed on a Perkin Elmer 241 polarimeter using a Na lamp. [$\alpha$] and c units are quoted as deg cm$^3$ g$^{-1}$ dm$^{-1}$ and g cm$^{-3}$, respectively. HPLC was carried out on an Agilent 1200 series running in normal phase under UV detection ($\lambda$ = 254 and 220 nm) using a ZORBAX RX-SIL (150 mm x 4.6 mm ID) as the analytical column. Semi-preparative HPLC was carried out using a ZORBAX RX-SIL (250 mm x 9.4 mm ID).

**Other techniques:** Reactions were monitored by thin layer chromatography on pre-coated aluminium-backed plates (Merck Kieselgel 60 with fluorescent indicator UV254). Spots were visualized either by UV or by staining with KMnO$_4$ or vanillin solutions. Flash column chromatography was performed using silica gel 60 (0.040 – 0.063 mm) (MN Kieselgel 60M).

**Materials:** All reagents, obtained from Acros, Aldrich, Fluka, Lancaster, Strem and Fluorochem fine chemicals suppliers, were used directly as supplied or purified by the methods described by Amerago and Chai. All non-aqueous reactions were performed in oven dried apparatus under argon or nitrogen atmospheres, using distilled anhydrous solvents, at room temperature unless otherwise indicated.
2. General procedures

**General Procedure A: Barbier Allylation**

The procedure of Otera et al. was used.\(^1\) To a mixture of tin powder (1.3 equiv.) and 2,3-dibromopropene (1.3 equiv.) in water / Et\(_2\)O (3 mL mmol\(^{-1}\), 1:1) was added HBr (48% aq., several drops) and the appropriate aldehyde (1.0 equiv.). The mixture was stirred overnight at rt before being diluted with water and extracted with Et\(_2\)O. The combined organic layers were dried (MgSO\(_4\)) and concentrated to afford the alcohol product, which was used without further purification, or purified by flash chromatography (ether or EtOAc / petroleum ether) for the purposes of characterization.

**General Procedure B: Mitsunobu Coupling and N-Boc deprotection**

The procedure of Lu and Li was used.\(^2\) Di-isopropylazodicarboxylate (1.5 equiv.) was added dropwise to a solution of triphenylphosphine (2.0 equiv.), TsNHBoc (1.3 equiv.) and the appropriate alcohol (1.0 equiv.) in THF (3 mL mmol\(^{-1}\)) at 0 °C. The reaction was stirred overnight at rt, before being concentrated. The residue was redisolved in Et\(_2\)O and then sonicated for 5 min; the resulting precipitate (triphenylphosphine oxide) was removed by filtration. To the filtrate was added hexanes, which was further sonicated for 5 min, and the resulting precipitate removed by filtration, before being concentrated. Purification of the residue by flash chromatography (typically petroleum ether / EtOAc, 20:1) afforded the N-Ts-N-Boc amide derivative. This was dissolved in CH\(_2\)Cl\(_2\) (2 mL mmol\(^{-1}\)), then TFA (0.5 mL mmol\(^{-1}\)) was added dropwise at 0 °C. The reaction mixture was stirred for (up to) 12 h at rt before being cooled to 0 °C, and slowly quenched by the dropwise addition of NaHCO\(_3\) (sat., aq.). The organic layer was separated, and the aqueous layer extracted with additional CH\(_2\)Cl\(_2\). The combined organic layers were dried (MgSO\(_4\)) and concentrated. Purification via flash chromatography (typically petroleum ether / EtOAc, 10:1→5:1) afforded the sulfonamide product.

**General procedure C: Bromination of alkynes via deprotonation with n-BuLi / quench with Br\(_2\)**

n-BuLi (2.5 M, 1.2 equiv.) was added dropwise to a stirred solution of the alkyne (1.0 equiv.) in THF (3 M) at −78 °C. The solution was stirred at −78 °C for 30 min, then bromine (1.4 equiv.) was added dropwise. The mixture was stirred for a further 15 min, before being quenched with Na\(_2\)S\(_2\)O\(_3\) (sat., aq.) and then warmed to rt. The reaction was extracted with Et\(_2\)O, and the combined organic layers dried (MgSO\(_4\)) and concentrated to afford the corresponding bromoalkyne, which was generally used without further purification. In cases where volatile bromoalkynes were prepared, some residual THF remained in the concentrate.
**General procedure D: Silver-catalyzed bromination of alkynes with NBS**

To a solution of terminal alkyne (1.0 equiv.) in acetone (1 mL mmol⁻¹) was added AgNO₃ (2.5 mol%). After stirring for 5 min, *N*-bromosuccinimide (1.1 equiv.) was added, and the mixture stirred for a further 4-15 h at rt until complete as judged by tlc. The mixture was then diluted with petroleum ether and filtered through a short silica pad (petroleum ether eluent). The resulting solution was concentrated, to obtain the corresponding bromoalkyne.

**General Procedure E: Preparation of bromoenynamides using the Hsung method[3]**

To a mixture of sulfonamide (1.0 equiv.), K₃PO₄ (2.0 equiv.), CuSO₄·5H₂O (0.2 equiv.) and 1,10-phenanthroline (0.4 equiv.) was added a solution of bromoalkyne (1.5 equiv.) in toluene (4 mL mmol⁻¹). The mixture was heated to 70 °C for 16 h before being cooled to rt and concentrated. Purification by flash chromatography (EtOAc / petroleum ether) afforded the bromoenynamide.

**General Procedure F: Stille cascade cyclisation to amidodienes**

To a reaction vessel containing PdCl₂(PPh₃)₂ (1 or 10 mol%) under Ar was added a degassed (Ar bubbling, 15 min) solution of the bromoenynamide (1.0 equiv.) and stannane coupling partner (1.6 equiv) in toluene (16.7 mL mmol⁻¹). The reaction mixture was then heated to 95 °C under Ar until the reaction was judged complete by TLC (4-24 h). The reaction was then cooled to rt, and concentrated. Purification via flash chromatography (EtOAc / petroleum ether eluent) afforded the bicyclic dienamide product.
**General Procedure G: Suzuki cascade cyclisation to amidodienes**

To a reaction vessel containing Pd(PPh₃)₄ (5 mol%) and Cs₂CO₃ (1.5 equiv.) under Ar was added a degassed (Ar bubbling, 15 min) solution of the bromoenynamide (1.0 equiv.) and vinylboronate (1.5 equiv.) in DME (16.7 mL·mmol⁻¹). The reaction mixture heated to reflux under Ar until the reaction was judged complete by TLC. The reaction was then cooled to rt and concentrated; purification via flash chromatography afforded the bicyclic dienamide product.

**General Procedure H: Reductive cyclization of bromoenynamides to pyrrolidines and piperidines (n = 1, 2)**

To a degassed (Ar bubbling, 15 min) solution of bromoenynamide (1.0 equiv.) in EtOH (0.045 M) was added Pd(PPh₃)₄ (2.5 mol%) and Cs₂CO₃ (1.5 equiv.). The reaction mixture was heated to 80 °C until judged complete by TLC, then it was cooled to rt and filtered through a Celite® plug (EtOAc eluent). The filtrate was concentrated, and the residue purified via column chromatography to afford the corresponding exocyclic diene product.

**General Procedure I: Reductive cyclization of bromoenynamides to piperidines (n = 2) and azepanes (n = 3)**

**Method A:** To a degassed (Ar bubbling, 15 min) solution of bromoenynamide (1.0 equiv.) in toluene / EtOH (10:1, 0.045 M) was added Pd(PPh₃)₄ (10 mol%) and K₂CO₃ (1.5 equiv.). The reaction mixture was heated to 80 °C until judged complete by TLC (3 x TLC runs on the same plate in 20:1 petroleum ether / EtOAc, to give separation of SM and product). The reaction was then cooled to rt and filtered through a Celite® plug (EtOAc eluent). The filtrate was concentrated, and the residue purified via flash chromatography to afford the corresponding exocyclic diene.

**Method B:** To a degassed (Ar bubbling, 15 min) solution of the appropriate bromoenynamide (1.0 equiv.) in toluene / EtOH (1:1, 0.045 M) was added Pd(PPh₃)₄ (2.5 mol%) and K₂CO₃ (1.5 equiv.). The reaction
mixture was heated to 80 °C until the reaction was judged complete by TLC (3 x TLC runs on the same plate in 20:1 petroleum ether / EtOAc to give separation). The reaction was then cooled to rt and filtered through a Celite® plug (EtOAc eluent). The filtrate was concentrated, and the residue purified via flash chromatography to afford the corresponding exocyclic diene.

**General Procedure J: Molander-Suzuki cascade cyclisation to amidodienes**

\[
\begin{align*}
3 & \xrightarrow{5 \text{ mol}\% \text{ Pd(PPh}_3)_4, \text{ LiOH (4 equiv.), MeCN / H}_2\text{O, 10:1, 85 °C}} 4 \\
\text{TsN} & \xrightarrow{1.1 \text{ equiv. KF}_3\text{B}} \text{R}^1 \xrightarrow{\text{R}^2} \text{R}^3
\end{align*}
\]

*NB. No precautions of anhydrous, degassed solvent or inert atmosphere were employed.*

To a mixture of ynamide (1 eq), potassium trifluoroborate (1.1 eq), LiOH (4 eq) and Pd(PPh₃)₄ (5 mol%) was added a solution of MeCN:H₂O (10:1) (5 mL/mmol), the mixture immersed in an oil bath at 85 °C and stirred rapidly for up to 3 h. The mixture was cooled to ambient temperature, diluted with Et₂O (5 mL/mmol) and NH₄Cl(aq) added. The product was extracted with Et₂O (∼2), dried (MgSO₄) and concentrated in vacuo, then purified via column chromatography (petroleum ether/Et₂O (9:1)).
3. Bromenynamide Synthesis

Preparation of alcohols 10a-c and ammonium salt 11:

Large scale synthesis of 2,3-dibromoprop-1-ene:

1,2,3-Tribromopropane

The procedure of Johnson and McEwen was used. To a three-necked flask equipped with stirrer bar was added allyl bromide (181.5 g, 1.50 mol, 1.0 equiv.) and CCl₄ (250 mL). The flask was fitted with a dropping funnel, calcium chloride exit tube and a thermometer. To the dropping funnel was added bromine (255.0 g, 1.60 mol, 1.1 equiv.), pre-washed with an equal volume of conc. H₂SO₄. The bromine was added dropwise to the cooled (−5 °C) solution of allylbromide such that the temperature never exceeded 0 °C. After addition, the reaction mixture was allowed to warm to rt and stirred for a further 30 min. The dropping funnel and thermometer were removed and replaced with glass stoppers, and the drying tube replaced with distillation apparatus. The reaction mixture was heated to 120 °C at atmospheric pressure, and then slowly to 150 °C to distil off the remaining bromine, allyl bromide and carbon tetrachloride. The collecting flask was replaced, and the pressure reduced to 26 mbar to remove the remaining starting materials and solvent until the thermometer registered a sudden rise in temperature, at which point only the 1,2,3-tribromopropane remained in the distilling flask, as a pale yellow oil (419 g, 1.49 mmol, 99%, used without further purification); Rf 0.33 (petroleum ether / EtOAc (10:1)); ¹H NMR (500 MHz, CDCl₃) δ_H 4.42 (1H, tt, J = 7.0, 4.0 Hz, H2), 3.99 (2H, dd, J = 7.0, 4.0 Hz, H1/H3), 3.90 (2H, dd, J = 7.0, 4.0 Hz, H1/H3); ¹³C NMR (125 MHz, CDCl₃) δ_C 48.7, 35.4. Data in accordance with literature values.
2,3-Dibromoprop-1-ene

\[ \text{Br} - \text{Br} \]

The procedure of Lespieau and Bourgeul was used for this reaction.\(^6\) To a round bottomed flask, connected to efficient distillation equipment, was added 1,2,3-tribromopropane (419 g, 1.49 mol, 1.0 equiv.), water (22 mL) and NaOH pellets (104 g, 2.61 mol, 1.75 equiv.). An exotherm was observed, then the mixture was heated further using a heat gun, with stirring, until vigorous ebullition occurs, whereupon spontaneous distillation of the product took place; the heat source was immediately removed. When the reaction subsided, the flask was heated as before and the mass became solid as the volatile components were removed. Once all volatile components were removed, the distillate was isolated and washed with water (150 mL). The lower (organic) layer was then distilled in vacuo to yield 2,3-dibromopropene as a colorless oil (203 g, 1.19 mmol, 80%); bp 68 °C at 75 mbar; \( R_f \) 0.54 (petroleum ether / EtOAc (10:1)); \( \text{IR} \) (thin film) \( \nu_{\text{max}} \) / cm\(^{-1}\) 2962, 1734, 1640, 1621, 1418, 1384, 1311, 1215, 1191, 1101, 938; \( ^1\text{H NMR} \) (400 MHz, CDCl\(_3\)) \( \delta \)H 6.03 (1H, dt, \( J = 2.0, 1.0 \) Hz, H1), 6.53 (1H, d, \( J = 2.0, H1' \)), 4.19 (2H, d, \( J = 1.0 \) Hz, H3); \( ^{13}\text{C NMR} \) (101 MHz, CDCl\(_3\)) 127.6, 121.2, 36.8; \( \text{HRMS} \) (CI) calc. for C\(_3\)H\(_4\)Br\(_2\) 197.8680, found 197.8684.

3-Bromobut-3-en-1-ol, 10a

\[ \text{OH} - \text{Br} \]

Route A: via 2,7-Dibromooccta-1,7-diene-4,5-diol S1. The procedure of Otera \textit{et al.} was used for this reaction.\(^7\) To a mixture of tin powder (29.7 g, 0.25 mol, 2.3 equiv.) and 2,3-dibromopropene (26 mL, 0.25 mol, 2.3 equiv.) in water / Et\(_2\)O (480 mL, 1:1) was added conc. aq. HBr (several drops) and aqueous glyoxal (12.6 mL, 0.11 mol, 40% wt, 1.0 equiv.). The resulting mixture was stirred overnight at rt before being diluted with water and extracted with Et\(_2\)O. The combined organic layers were dried (MgSO\(_4\)) and the solvent removed in vacuo to afford diol S1 as a coarse white powder (34.0 g, 0.25 mol, quant., unassigned mixture of diastereoisomers) which was used without further purification, but could be purified by flash chromatography (petroleum ether / ethyl acetate, 3:1) for the purposes of characterization; mp 85-86 °C; \( R_f \) 0.12 (petroleum ether / ethyl acetate, 3:1); \( \text{IR} \) (thin film) \( \nu_{\text{max}} \) / cm\(^{-1}\) 3335, 2914, 1632, 1409, 1199, 1106, 898; \( ^1\text{H NMR} \) (400 MHz, CDCl\(_3\)) \( \delta \)H 5.76 (2H, app s, H1/H8), 5.59 (2H, t, \( J = 2.0 \) Hz, H1'/H8'), 4.05 (1H, m, H4/H5), 3.91 (1H, m, H4/H5), 2.77 (2H, m, H3/H6), 2.66 (2H, m, H3/H6); \( ^{13}\text{C NMR} \) (101 MHz, CDCl\(_3\)) \( \delta \)C 130.4, 130.3, 120.8, 120.6, 71.5, 70.9, 46.4, 44.4; \( \text{HRMS} \) (ES\^+) calc. for C\(_8\)H\(_{11}\)Br\(_2\)O\(_2\) [M-H]\(^-\) 298.9144; found 298.9103.

To a solution of S1 (7.60 g, 25.0 mmol, 1.0 equiv.) in MeOH / pH 7 buffer (108 mL, 5:1) was added NaIO\(_4\) (8.13 g, 38.0 mmol, 1.5 equiv.). The reaction mixture was stirred at rt for 2 h, then cooled to 0 °C; to this was added NaBH\(_4\) (1.93 g, 51.0 mmol, 2.0 equiv.) portionwise. Once the addition was complete, the reaction was allowed to warm to rt and stirred for 20 min, before being quenched with water. The mixture was extracted with CH\(_2\)Cl\(_2\) and the combined organic layers dried (MgSO\(_4\)) and concentrated. The crude product was
purified by distillation to afford 10a as a colorless liquid (5.12 g, 16.5 mmol, 66%); bp 74 °C @ 20 mbar; Rf 0.21 (petroleum ether / Et2O, 1:1); 1H NMR (400 MHz, CDCl3) δH 5.71 (1H, app s, H4), 5.53 (1H, app s, H4), 3.81 (2H, app q, J = 6.0 Hz, H1), 2.67 (2H, t, J = 6.0 Hz, H2), 1.87 (1H, t, J = 6.0 Hz, OH); 13C NMR (101 MHz, CDCl3) δC 130.6, 119.5, 60.2, 44.5. Data in accordance with literature values.\[8\] Note: the alcohol decomposes during distillation if attempted at higher temperatures than above.

Route B: Prepared by General Procedure A using dibromopropene (44.0 mL, 0.43 mol) formaldehyde (19.4 mL, 0.33 mol, 37% in H2O) to give 10a as a pale yellow oil (48.8 g, 0.32 mol, 97%). Data as above.

5-Bromohex-5-en-3-ol, 10b

Prepared by General Procedure A using propionaldehyde (0.25 mL, 3.44 mmol) to afford 10b as a colorless oil (572 mg, 3.16 mmol, 92%); Rf 0.23 (petroleum ether / EtOAc, 10:1); 1H NMR (500 MHz, CDCl3) δH 5.70 (1H, app s, H6), 5.55 (1H, app s, H6), 3.88-3.84 (1H, m, H3), 2.58 (1H, dd, J = 14.5, 4.0 Hz, H4), 2.51 (1H, dd, J = 14.5, 8.5 Hz, H4), 1.75 (1H, br s, OH), 1.57-1.49 (2H, m, H2), 0.99 (3H, t, J = 7.5 Hz, H1); 13C NMR (125 MHz, CDCl3) δC 130.9, 119.6, 70.4, 49.0, 29.3, 9.9. Data in accordance with literature values.\[9\]

3-Bromo-1-(4-fluorophenyl)but-3-en-1-ol, 10c

Prepared by General Procedure A using 4-fluorobenzaldehyde (5.20 mL, 48.2 mmol) to afford 10c as a pale pink oil (7.63 g, 42.4 mmol, 88%); Rf 0.21 (petroleum ether / EtOAc, 10:1); 1H NMR (200 MHz, CDCl3) δH 7.38-7.33 (2H, m, ArH), 7.09-7.02 (2H, m, ArH), 5.67 (1H, app s, H4), 5.55 (1H, d, J = 1.5 Hz, H4), 5.04 (1H, dd, J = 8.5, 4.5 Hz, H1), 2.84 (1H, ddd, J = 14.5, 8.5, 1.0 Hz, H2), 2.72 (1H, ddd, J = 14.5, 4.5, 1.0 Hz, H2); 13C NMR (101 MHz, CDCl3) δC 162.3 (d, J_C,F = 245.8 Hz), 138.6, 129.8, 127.5 (d, J_C,F = 8.1 Hz), 120.2, 115.3 (d, J_C,F = 21.4 Hz), 71.0, 51.2. Data in accordance with literature values.\[10\]

3-Bromobut-3-en-1-yl 4-methylbenzenesulfonate, S2

To an ice-cooled solution of alcohol 10a (5.11 g, 33.8 mmol, 1.0 equiv.) in CH2Cl2 (2.6 mL) was added pyridine (5.5 mL, 67.7 mmol, 2.0 equiv.) and p-toluenesulfonyl chloride (9.68 g, 50.8 mmol, 1.5 equiv.). After addition, the reaction was warmed to rt and stirred for 3 h before being diluted with CH2Cl2. The organic layer was separated and washed with HCl (1M, aq.). The aqueous layer was extracted with CH2Cl2,
and the combined organics washed with NaHCO$_3$ (sat., aq.), dried (MgSO$_4$) and concentrated. Purification via flash chromatography (petroleum ether / Et$_2$O, 8:1) afforded tosylate S2 as a colorless oil (10.3 g, 33.8 mmol, quant.); R$_f$ 0.21 (petroleum ether / Et$_2$O, 8:1); $^1$H NMR (400 MHz, CDCl$_3$) δ$_H$ 7.79 (1H, d, J = 8.0 Hz, ArH), 7.35 (2H, d, J = 8.0 Hz, ArH), 5.65 (1H, app s, H$_4$), 5.48 (1H, d, J = 2.0 Hz, H$_4$), 4.19 (2H, t, J = 6.2 Hz, H$_2$), 2.74 (2H, t, J = 6.2 Hz, H$_2$), 2.45 (3H, s, TsCH$_3$); $^{13}$C NMR (101 MHz, CDCl$_3$) δ$_C$ 145.0, 132.8, 129.9, 128.0, 127.6, 120.2, 67.2, 40.7, 21.7. Data in accordance with literature values.$^{[11]}$

4-Azido-2-bromobut-1-ene, S3

![4-Azido-2-bromobut-1-ene](image)

The procedure of Pillai was used for this reaction.$^{[11]}$ To sodium azide (1.46 g, 22.5 mmol, 2.0 equiv.) at rt was added a solution of tosylate S2 (3.43 g, 11.2 mmol, 1.0 equiv.) in DMSO (12.7 mL). After stirring overnight, water was added and the mixture extracted with Et$_2$O. The combined organic extracts were dried (MgSO$_4$) and concentrated in vacuo to afford azide S3 as a yellow oil (1.64 g, 9.33 mmol, 83%) which was used without further purification; R$_f$ 0.52 (petroleum ether / Et$_2$O, 8:1); $^1$H NMR (400 MHz, CDCl$_3$) δ$_H$ 5.73 (1H, br s, H$_1$), 5.55 (1H, br d, J = 1.0 Hz, H$_1$), 3.50 (2H, t, J = 6.5 Hz, H$_4$), 2.68 (2H, t, J = 6.5 Hz, H$_3$); $^{13}$C NMR (101 MHz, CDCl$_3$) δ$_C$ 129.7, 119.6, 49.0, 40.8. Data in accordance with literature values.$^{[11]}$

3-Bromobut-3-en-1-aminium acetate, 11, and 3-bromobut-3-en-1-amine, S4

![3-Bromobut-3-en-1-aminium acetate](image)

The procedure of Pillai was used for this reaction.$^{[11]}$ Hydrogen sulfide was bubbled through a solution of azide S3 (1.94 g, 11.0 mmol) in pyridine / water (40 mL, 1:1). After 2 h, 2N acetic acid was added until the reaction was neutralized, and the mixture was then concentrated in vacuo, then azeotroped several times with EtOH. The resulting brown oil was dissolved in water, filtered, and concentrated in vacuo, co-evaporating several times with toluene, to give the amine salt 11 as a brown oil (1.79 g, 8.48 mmol, 77%); $^1$H NMR (400 MHz, D$_2$O) 5.70 (1H, app s, H$_4$), 5.50 (1H, app s, H$_4$), 4.67 (3H, br, NH$_3^+$), 3.07 (3H, s, OAc), 2.66 (2H, t, J = 6.5 Hz, H$_2$), 1.78 (3H, s, OAc); $^{13}$C NMR (101 MHz, D$_2$O) δ$_C$ 180.4, 127.9, 121.6, 38.7, 37.8, 23.0. Data in accordance with literature values.$^{[11]}$

For subsequent reactions of the free amine (vide infra), 11 was partitioned between sat. aq. NaOH and CH$_2$Cl$_2$, and the organic layers combined, dried (MgSO$_4$) and concentrated in vacuo to afford the amine S4; R$_f$ 0.19 (petroleum ether / EtOAc, 1:1); $^1$H NMR (500 MHz, CDCl$_3$) δ$_H$ 5.64 (1H, appt s, H$_4$), 5.49 (1H, appt s, H$_4$), 2.90 (2H, t, J = 6.1 Hz, H$_1$), 2.53 (2H, t, J = 6.1 Hz, H$_2$); $^{13}$C NMR (125 MHz, CDCl$_3$) δ$_C$ 131.9, 118.6, 45.3, 39.8. Data in agreement with literature values.$^{[12]}$
Preparation of amide derivatives 9a-h:

**General Procedure B**

1. TsBocNH, PPh₃, DIAD
2. TFA

TsCl, Et₃N

TFA, py

Boc₂O, Et₃N, DMAP

MeO₂COCl, py

BocHN

NH₂

BocHN

NH₂

**Method A:** To a stirred solution of the free amine S₄ (derived from 11 as above, 200 mg, 1.33 mmol, 1.0 equiv.) and triethylamine (0.74 mL, 5.33 mmol, 4.0 equiv.) in CH₂Cl₂ (4 mL) at 0 °C, was added p-toluenesulfonyl chloride (253 mg, 1.33 mmol, 1.0 equiv.). Upon completion as judged by TLC, the reaction mixture was diluted with CH₂Cl₂ and washed with 1 M HCl. The aqueous layer was extracted with CH₂Cl₂ and the combined organic phases were washed with NaHCO₃ (sat., aq.), dried (MgSO₄) and concentrated to afford sulfonamide 9a as a pale yellow oil (358 mg, 1.18 mmol, 89%) which was of a sufficient purity to be used without further purification.

**Method B:** Prepared by General Procedure B using 3-bromobut-3-en-1-ol 10a (5.57 g, 36.9 mmol) to afford sulfonamide 9a as a colorless oil, which solidified on storage to a cream colored solid (7.43 g, 24.0 mmol, 65%); **mp** 44-45 °C; **Rf** 0.13 (petroleum ether / EtOAc, 5:1); **IR** (thin film) ν max / cm⁻¹ 3261, 1629, 1598, 1423, 1317, 1163; **¹H NMR** (400 MHz, CDCl₃) δ H 7.76 (2H, d, J = 8.5 Hz, ArH), 7.32 (2H, d, J = 8.5 Hz, ArH), 5.60 (1H, app. s, H₄), 5.48 (1H, d, J = 1.5 Hz, H₄), 4.83 (1H, br t, J = 6.0 Hz, NH), 3.16 (2H, t, J = 6.5 Hz, H₁), 2.57 (2H, t, J = 6.5 Hz, H₂), 2.43 (3H, s, TsCH₃); **¹³C NMR** (101 MHz, CDCl₃) δ C 143.6, 136.9, 129.8, 129.6, 127.1, 120.0, 41.3, 41.0, 21.5; **HRMS** (ES+) calc. for C₁₁H₁₅⁸¹BrNO₂S [M+H]⁺ 305.9981; found 305.9965.
**N-(5-Bromohex-5-en-3-yl)-4-methylbenzenesulfonamide, 9b**

Prepared by General Procedure B using 10b (572 mg, 3.01 mmol) to afford the sulfonamide 225b as a colorless oil (425 mg, 1.28 mmol, 42%); Rf 0.06 (petroleum ether / EtOAc, 10:1); IR (thin film) νmax / cm⁻¹ 3281, 1631, 1599, 1451, 1430, 1324, 1158, 1093, 1068, 893; ¹H NMR (500 MHz, CDCl₃) δ H 7.78 (2H, d, J = 8.0 Hz, ArH), 7.31 (2H, d, J = 8.0 Hz, ArH), 5.56 (1H, app s, H6), 5.40 (1H, app s, H6), 4.46 (1H, d, J = 8.0 Hz, NH), 3.47 (1H, app sex tet, J = 6.5 Hz, H3), 2.52 (1H, dd, J = 14.5, 6.5 Hz, H4), 2.45 (1H, dd, J = 14.5, 7.0 Hz, H4), 2.44 (3H, s, TsC₃H₃), 1.64-1.61 (1H, m, H2), 1.42 (1H, app sept, J = 7.0 Hz, H2), 0.83 (3H, t, J = 7.5 Hz, H1); ¹³C NMR (125 MHz, CDCl₃) δ C 143.4, 137.8, 129.7, 129.6, 127.3, 120.1, 53.6, 46.4, 26.9, 21.6, 9.5; HRMS (ES⁺) calcd. for C₁₃H₁₈BrNNaO₂ [M+Na]⁺ 354.0134; found 354.0122.

**N-(3-Bromo-1-(4-fluorophenyl)but-3-en-1-yl)-4-methylbenzenesulfonamide, 9c**

Prepared by General Procedure B using 10c (2.00 g, 8.16 mmol) to afford sulfonamide 9c as a pale yellow oil (1.99 g, 4.90 mmol, 60%); Rf 0.29 (petroleum ether / EtOAc, 3:1); IR (thin film) νmax / cm⁻¹ 3373, 2911, 1629, 1509, 1223, 1157; ¹H NMR (200 MHz, CDCl₃) δ H 7.58 (2H, d, J = 8.5 Hz, TsH), 7.18 (2H, d, J = 8.5 Hz, TsH), 7.09-7.06 (2H, m, 4-FPhH), 6.88 (2H, t, J = 8.5 Hz, 4-FPhH), 5.51 (1H, dt, J = 2.0, 1.0 Hz, H4), 5.40 (1H, d, J = 2.0 Hz, H4), 5.06 (1H, d, J = 5.5 Hz, Nh), 4.59 (1H, q, J = 6.5 Hz, H1), 2.82 (1H, ddd, J = 14.5, 8.0, 1.0 Hz, H2), 2.70 (1H, ddd, J = 14.5, 6.0, 1.0 Hz, H2), 2.40 (3H, s, TsC₃H₃); ¹³C NMR (101 MHz, CDCl₃) δ C 162.2 (d, JCF = 246.6 Hz), 143.5, 136.8, 135.1 (d, JCF = 3.1 Hz), 129.4, 128.4, 128.4, 127.3, 120.9, 115.4 (d, JCF = 21.7 Hz), 55.6, 49.2, 21.5. HRMS (FI⁺) calcd. for C₁₀H₁₂⁷⁹BrFN [M+H]⁺ 244.0132; found 244.0121.

**tert-Butyl (3-bromobut-3-en-1-yl)carbamate, 9d**

To a solution of free amine S4 (derived from 11 as above, 200 mg, 1.33 mmol, 1.0 equiv.) in THF (5 mL) was added triethylamine (0.09 mL, 0.66 mmol, 0.5 equiv.) and di-tert-butyl dicarbonate (Boc₂O, 275 mg, 1.26 mmol, 0.95 equiv.). The reaction mixture was stirred at rt for 24 h before the addition of DMAP (16 mg, 0.13 mmol, 0.1 equiv.). After stirring at rt for a further 48 h the reaction was heated to reflux for 5 h. Upon completion as judged by TLC, the reaction was cooled to rt and quenched with 1 M HCl. The mixture was extracted with CH₂Cl₂, and the combined organic layers were dried (MgSO₄) and concentrated, to afford 9d as a brown oil (210 mg, 0.84 mmol, 63%) which was used without further purification, but could be purified...
by flash chromatography for the purposes of characterization: \( R_f \) 0.55 (petroleum ether / EtOAc, 10:1); \( \text{IR} \) (thin film) \( \nu_{\text{max}} / \text{cm}^{-1} \): 3351, 2977, 1698, 1630, 1519, 1366, 1251; \( ^1\text{H NMR} \) (400 MHz, CDCl\(_3\)) \( \delta_H \): 5.64 (1H, app s, H4), 5.49 (1H, app s, H4), 4.68 (1H, br, \( \text{NH} \)), 3.33 (2H, d, \( J = 6.0 \text{ Hz, H1} \)), 2.61 (2H, t, \( J = 6.0 \text{ Hz, H2} \)), 1.43 (9H, s, \( \text{t-Bu} \)); \( ^{13}\text{C NMR} \) (101 MHz, CDCl\(_3\)) \( \delta_C \): 155.8, 131.0, 119.0, 79.4, 41.9, 38.6, 28.4; \( \text{HRMS} \) (ES+) calc. for C\(_9\)H\(_{16}\)BrNNaO\(_2\) \([\text{M+Na}^+]\) 272.0257; found 272.0257.

**Methyl (3-bromobut-3-en-1-yl)carbamate, 9e**

\[
\text{MeO}_2\text{CHN} \quad \text{Br}
\]

To a solution of free amine S4 (50 mg, 0.33 mmol, 1.0 equiv.) in CH\(_2\)Cl\(_2\) (1 mL) was added pyridine (54 \( \mu \)L, 0.66 mmol, 2.0 equiv.) then methyl chloroformate (31 \( \mu \)L, 0.40 mmol, 1.2 equiv.). The resulting reaction mixture was stirred at rt overnight, and then was diluted with CH\(_2\)Cl\(_2\) and washed with 1 M HCl. The aqueous layer was extracted with CH\(_2\)Cl\(_2\) and the combined organic phases washed with NaHCO\(_3\) (sat. aq.), dried (MgSO\(_4\)) and concentrated to afford 9e as a colorless oil (56 mg, 0.27 mmol, 81%), which was used without further purification, but could be purified by flash chromatography for the purposes of characterization: \( R_f \) 0.57 (petroleum ether / EtOAc, 2:1); \( ^1\text{H NMR} \) (400 MHz, CDCl\(_3\)) \( \delta_H \): 5.65 (1H, app s, H4), 5.50 (1H, app s, H4), 4.87 (1H, br s, \( \text{NH} \)), 3.66 (3H, s, CO\(_2\)CH\(_3\)), 3.39 (2H, q, \( J = 6.0 \text{ Hz, H1} \)), 2.62 (2H, t, \( J = 6.0 \text{ Hz, H2} \)); \( ^{13}\text{C NMR} \) (101 MHz, CDCl\(_3\)) \( \delta_C \): 156.9, 130.8, 119.2, 52.1, 41.5, 38.9; \( \text{HRMS} \) (FI\(^+\)) calc. for C\(_6\)H\(_{10}\)BrNO \([\text{M}]^+\) 206.9895, found 206.9889.

**N-(3-Bromobut-3-en-1-yl)-2,2,2-trifluoroacetamide, 9f**

\[
\text{F}_3\text{C} \quad \text{NH} \quad \text{Br}
\]

To a solution of free amine S4 (145 mg, 0.97 mmol, 1.0 equiv.) in CH\(_2\)Cl\(_2\) (2 mL) at 0 °C was added pyridine (0.16 mL, 1.94 mmol, 2.0 equiv.) and then trifluoroacetic anhydride (0.16 mL, 1.16 mmol, 1.2 equiv.). The resulting mixture was warmed to rt and stirred overnight before being diluted with CH\(_2\)Cl\(_2\) and washed with 1 M HCl. The aqueous layer was extracted with CH\(_2\)Cl\(_2\) and the combined organic phases washed with NaHCO\(_3\) (sat. aq.), dried (MgSO\(_4\)) and concentrated to afford 9f as a brown oil (140 mg, 0.57 mmol, 59%), which was of sufficient purity to be used without further purification, but could be purified by flash chromatography for the purposes of characterization: \( R_f \) 0.69 (petroleum ether / EtOAc, 2:1); \( \text{IR} \) (thin film) \( \nu_{\text{max}} / \text{cm}^{-1} \): 3313, 3104, 2951, 1708, 1632, 1560, 1432, 1185; \( ^1\text{H NMR} \) (400 MHz, CDCl\(_3\)) \( \delta_H \): 6.60 (1H, br s, \( \text{NH} \)), 5.69 (1H, app s, H4), 4.87 (1H, br s, H4), 3.60 (3H, s, CO\(_2\)CH\(_3\)), 3.39 (2H, q, \( J = 6.0 \text{ Hz, H1} \)), 2.62 (2H, t, \( J = 6.0 \text{ Hz, H2} \)); \( ^{13}\text{C NMR} \) (101 MHz, CDCl\(_3\)) \( \delta_C \): 157.7, 129.6, 120.2, 114.3 (q, \( J = 287 \text{ Hz} \)), 40.2, 37.9; \( \text{HRMS} \) (ES\(^–\)) calc. for C\(_6\)H\(_6\)BrF\(_3\)NO \([\text{M-H}]^–\) 243.9590; found 243.9589.
**tert-Butyl pent-4-yn-1-yl(tosyl)carbamate (S5)**

\[
\text{Di-iso-propylazodicarboxylate} \ (0.72 \text{ g, 3.57 mmol, 1.5 equiv.}) \text{ was added dropwise to a stirred solution of PPh}_3 \ (1.25 \text{ g, 4.77 mmol, 2.0 equiv.}), \text{TsNHBOc} \ (0.84 \text{ g, 3.9 mmol, 1.3 equiv.}) \text{ and 4-pentyn-1-ol} \ (0.22 \text{ mL, 2.38 mmol, 1.0 equiv.}) \text{ in THF} \ (7 \text{ mL}) \text{ at 0 }^\circ\text{C. The reaction was warmed to rt, and stirred overnight, then concentrated. The residue was purified by flash chromatography (petroleum ether / EtOAc, 10:1) to give N-Boc-N-Ts amide S5 as a white solid (768 mg, 2.28 mmol, 95%); mp 97.4-100.6 °C; Rf 0.27 (petroleum ether / EtOAc, 5:1); IR (thin film) \nu_{max} / \text{cm}^{-1} 3278, 3007, 2984, 2960, 2929, 1726, 1597, 1443, 1369, 1346, 1320, 1257, 1118; ^1H NMR (400 MHz, CDCl}_3 \delta_{H} 7.78 (2H, d, J = 8.5 Hz, TsH), 7.30 (2H, d, J = 8.0 Hz, TsH), 3.92 (2H, app dd, J = 8.0, 7.0 Hz, H1), 2.44 (3H, s TsCH}_3, 2.28 (2H, td, J = 7.0, 2.5 Hz, H3), 1.99 (2H, app quin, J = 7.0 Hz, H2), 1.98 (1H, t, J = 2.5 Hz, H5), 1.34 (9H, s, t-Bu); ^13C NMR (101 MHz, CDCl}_3 \delta_{C} 144.3, 137.5, 129.4, 128.0, 84.4, 83.2, 69.1, 46.4, 29.0, 28.0, 21.8, 16.2; HRMS (ES\textsuperscript{+}) calc. for C\textsubscript{17}H\textsubscript{23}NNaO\textsubscript{4}S\textsuperscript{+} [M+Na\textsuperscript{+}]\textsuperscript{+} 360.1240; found 360.1237.**

**N-(4-Bromopent-4-en-1-yl)-4-methylbenzenesulfonamide, 9g**

A modified procedure of Moran and Morken was used\[13\]. To an oven-dried flask equipped with a stirrer bar was added \text{BBr}_3 (9.05 mL, 9.05 mmol, 1 M in CH\textsubscript{2}Cl\textsubscript{2}, 0.5 equiv.). The solution was cooled to −78 °C, before the dropwise addition of a solution of alkyne S5 (6.11 g, 18.1 mmol, 1.0 equiv.) in CH\textsubscript{2}Cl\textsubscript{2} (30 mL). The reaction mixture was allowed to warm to rt over 4.5 h, then glacial AcOH (19 mL) was added. After stirring for a further 1 h, the reaction was quenched by the addition of water and then extracted with CH\textsubscript{2}Cl\textsubscript{2} (x 3). The combined organic layers were dried (MgSO\textsubscript{4}), filtered and concentrated. Purification via flash chromatography (petroleum ether / EtOAc, 10:1→3:1) afforded 9g as a light brown oil (2.57 g, 7.96 mmol, 44%); Rf 0.13 (petroleum ether / EtOAc + 1% NEt\textsubscript{3}, 10:1); \^1H NMR (200 MHz, CDCl\textsubscript{3}) \delta_{H} 7.75 (2H, d, J = 8.5 Hz, TsH), 7.30 (2H, d, J = 8.0 Hz, TsH), 5.54 (1H, m, H5), 5.36 (1H, d, J = 2.0 Hz, H5), 5.03 (1H, br s, NH), 2.94 (2H, q, J = 6.5 Hz, H1), 2.42 (5H, m, TsCH\textsubscript{3} and H3), 1.72 (2H, qu, J = 7.0 Hz, H2). Data in accordance with literature values\[14\].

**tert-Butyl N-hex-5-ynyl-N-(p-tolylsulfonyl)carbamate (S6)**

Di-iso-propylazodicarboxylate (3.09 g, 15.3 mmol, 1.5 equiv.) was added dropwise to a stirred solution of PPh\textsubscript{3} (5.34 g, 20.4 mmol, 2.0 equiv.), TsNHBoc (3.59 g, 13.2 mmol, 1.3 equiv.) and 5-hexyn-1-ol (1.0 g, 10.2 mmol, 1.0 equiv.) in THF (7 mL) at 0 °C. The reaction was warmed to rt and stirred overnight, then
concentrated. The residue was purified by flash chromatography (petroleum ether → petroleum ether / EtOAc, 4:1) to give N-Boc-N-Ts amide S6 as a white solid (3.31 g, 9.43 mmol, 93%); mp 65.3-67.9 °C; Rf 0.41 (petroleum ether / EtOAc, 5:1); IR (thin film) ν <sub>max</sub> / cm<sup>-1</sup> 3286, 2979, 1598, 1456, 1352, 1289, 1256, 1184, 1087; ¹H NMR (400 MHz, CDCl<sub>3</sub>) δ<sub>H</sub> 7.78 (2H, d, J = 8.0 Hz, TsH<sub>2</sub>), 7.30 (2H, d, J = 8.0 Hz, TsH), 3.85 (2H, t, J = 7.0, 2.5 Hz, H4), 2.26 (2H, td, J = 7.0, 2.5 Hz, H4), 1.97 (1H, t, J = 2.5 Hz, H6), 1.88 (2H, qu, J = 7.5 Hz, H2), 1.60 (2H, app quin, J = 7.5 Hz, H3), 1.34 (9H, s, t-Bu); ¹³C NMR (101 MHz, CDCl<sub>3</sub>) δ<sub>C</sub> 151.0, 144.1, 137.4, 129.2, 127.8, 84.2, 84.0, 68.7, 46.6, 29.3, 27.9, 25.6, 21.6, 18.1; HRMS (ES+) calc. for C<sub>18</sub>H<sub>23</sub>NaO<sub>4</sub>S [M+Na]<sup>+</sup> 374.1397; found 374.1391.

**N-(5-Bromohex-5-en-1-yl)-4-methylbenzenesulfonamide, 9h**

A modified procedure of Moran and Morken was used<sup>[13]</sup>. To an oven-dried flask equipped with a stirrer bar was added BBr<sub>3</sub> (0.14 mL, 0.14 mmol, 1 M in CH<sub>2</sub>Cl<sub>2</sub>, 0.5 equiv.). The solution was cooled to ~78 °C, before the dropwise addition of a solution of alkyne S6 (100 mg, 0.28 mmol, 1.0 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (0.5 mL). The reaction mixture was allowed to warm to rt over 4.5 h, then glacial AcOH (0.3 mL) was added. After stirring for a further 1 h, the reaction was quenched by the addition of water and then extracted with CH<sub>2</sub>Cl<sub>2</sub> (x 3). The combined organic layers were dried (MgSO<sub>4</sub>), filtered and concentrated. Purification via flash chromatography (petroleum ether / EtOAc, 10:1 → 3:1) afforded 9h as a colorless oil (37 mg, 0.086 mmol, 30%); Rf 0.10 (petroleum ether / EtOAc, 10:1); IR (thin film) ν <sub>max</sub> / cm<sup>-1</sup> 3279, 2941, 2867, 1630, 1599, 1433, 1156, 1093, 887; ¹H NMR (500 MHz, CDCl<sub>3</sub>) δ<sub>H</sub> 7.75 (2H, d, J = 8.0 Hz, TsH<sub>2</sub>), 7.32 (2H, d, J = 8.0 Hz, TsH), 5.52 (1H, app s, H6), 5.37 (1H, app s, H6), 4.60 (1H, t, J = 6.0 Hz, NH), 2.96 (2H, app q, J = 6.5 Hz, H1), 2.44 (3H, s, TsCH<sub>3</sub>), 2.37 (2H, t, J = 7.0 Hz, H4), 1.55-1.46 (4H, m, H2 and H3); ¹³C NMR (125 MHz, CDCl<sub>3</sub>) δ<sub>C</sub> 143.5, 137.0, 133.8, 129.8, 127.1, 117.0, 42.9, 40.7, 28.3, 24.8, 21.6; HRMS (ES+) calc. for C<sub>13</sub>H<sub>18</sub>BrNNaO<sub>4</sub>S [M+Na]<sup>+</sup> 354.0134, found 354.0127. (This compound was made in higher yield by Mitsunobu reaction / deprotection on 5-bromohex-5-en-1-ol; Mitsunobu yield 59%; TFA deprotection 88%), according to General Procedure B.

**Preparation and use of N-(2-bromoallyl)-4-methyl-N-(2-(4-methylphenylsulfonamido)ethyl)benzene sulfonamide, 9i**

To a rapidly stirring solution of N-(2-(((tert-butyl(dimethyl)silyl)oxy)ethyl)-4-methylbenzenesulfonamide<sup>[15]</sup> (2.63 g, 7.98 mmol) in PhMe (80 mL) was added tetrabutylammonium hydrogensulfate (271 mg, 0.798 mmol), followed by a solution of NaOH (80 mL of a 25% w/v q. solution). The mixture was stirred
rapidly for 45 min, then the layers were separated and the organic phase was washed with NH₄Cl (30 mL, sat., aq.). The organic phase was dried (MgSO₄) and concentrated to afford the crude product as a pale yellow semi-solid, which was purified by rapid flash chromatography (7%→12% EtOAc / petroleum ether) to afford intermediate **12** as a colorless oil (3.38 g, 7.54 mmol, 94%) that was used immediately in the subsequent steps. *Note: 12 decomposes on standing when neat. To a solution of N-(2-bromoallyl)-N-(2-((tert-butyldimethylsilyl)oxy)ethyl)-4-methylbenzenesulfonamide **12** (3.00 g, 6.69 mmol) in THF (75 mL) at 0 °C was added TBAF (6.8 mL of a 1 M solution in THF, 6.8 mmol), and the reaction was stirred for 1 h. The reaction was then quenched with NH₄Cl (30 mL, sat., aq.) and extracted with Et₂O (2 × 30 mL). The combined organic fractions were dried (Na₂SO₄), filtered and concentrated to afford the crude alcohol N-(2-bromoallyl)-N-(2-hydroxyethyl)-4-methylbenzenesulfonamide as a colorless oil (2.07 g, ~93%) which was used immediately in the subsequent reaction. To a solution of PPh₃ (1.70 g, 6.48 mmol) in THF (30 mL) at 0 °C was added DIAD (1.12 mL, 5.69 mmol) steadily, and the mixture stirred for 20 min. A solution of crude deprotected alcohol (1.80 g, 5.39 mmol) in THF (10 mL) was added dropwise, then the mixture was stirred for 10 min. BocNHTs (1.47 g, 5.42 mmol) was added in one portion and the mixture warmed to rt over 16 h. The mixture was concentrated, then redissolved in a minimal volume of CHCl₃ and then filtered rapidly through a pad of silica, eluting with 1.6% v/v acetone / CHCl₃, then concentrated *in vacuo* to afford the tert-butyl ((N-(2-bromoallyl)-4-methylphenyl)sulfonyl)amido)ethyl)(tosyl)carbamate **S7** (2.45 g) as an unstable colorless oil; Rf 0.31 (1.6% v/v acetone / CHCl₃).¹H NMR (400 MHz, CDCl₃) δH 7.79 (2H, d, J = 8.5 Hz, TsH), 7.78 (2H, d, J = 8.5 Hz, TsH), 7.33 (2H, d, J = 8.5 Hz, TsH), 7.32 (2H, d, J = 8.5 Hz, TsH), 5.93-5.89 (1H, m, C=CHH), 5.65 (1H, br d, J = 2.0 Hz, C=CHH), 4.16 (2H, s, TsNCH₂C(Br)=CH₂), 4.01-3.95 (2H, m, TsBocNCH₂), 3.49-3.44 (2H, m, TsBocNCH₂CH₂), 2.45 (3H, s, TsMe), 2.44 (3H, s, TsMe), 1.39 (9H, s, OC(CH₃)₃). This intermediate **S7** (2.45 g) was immediately redissolved in CH₂Cl₂ (37 mL) and treated with TFA (37 mL). After 1 h, the organic fraction was washed successively with H₂O (50 mL) and NaHCO₃(aq) (30 mL), then dried (Na₂SO₄), filtered and concentrated *in vacuo* to afford the crude sulfonamide product **9i** as a colorless oil (1.97 g, ~75% over three steps). *Note: Throughout this procedure, concentration in vacuo must be carried out with bath temperature <20 °C to minimize decomposition.* Sulfonamide **9i** undergoes ready decomposition upon concentration and in neutral solution, so must be stored below ~20 °C or used immediately.

![Diagram](image)

**3I**

**Formation of ynamide 3I:** To a mixture of crude tosylamide **9i** (1.00 g, 2.05 mmol), K₂PO₄ (870 mg, 4.10 mmol), 1,10-phenanthroline (296 mg, 1.64 mmol), CuSO₄•5H₂O (205 mg, 0.821 mmol) and 1-bromo-1-octyne (545 mg, 2.88 mmol) was added anhydrous PhMe (10 mL) and the mixture heated to 70 °C for 16 h. The mixture was cooled to rt and passed through cotton wool, eluting with Et₂O, then organic concentrated. Purification by flash chromatography (petroleum ether / EtOAc (4:1)) afforded the ynamide **3I**
To a solution of 1-aminopropanol (5.00 g, 66.0 mmol) in CHCl₃ (10 mL) at 0 °C was added Et₃N (25.6 mL, 133 mmol), followed by a solution of tosyl chloride (13.8 g, 72.6 mmol) in CHCl₃ (15 mL) over a period of 10 min. The mixture was warmed slowly to rt, then quenched with NaHCO₃ (25 mL of a 5% w/v aq. solution), and EtOAc (50 mL) was added. The layers were separated and the organic phase was washed with citric acid (2 × 20 mL, 5% w/v aq. solution) then brine (20 mL). The organic phase was dried (MgSO₄) and concentrated to afford the crude tosylated product as a pale yellow semi-solid (13.4 g, ~88%).

To a solution of PPh₃ (2.06 g, 7.85 mmol) in THF (30 mL) at 0 °C was added DIAD (1.35 mL, 6.87 mmol) steadily, and the mixture stirred for 15 min. A solution of crude tosylated product (1.50 g, 6.54 mmol) in THF (30 mL) was added dropwise, then the mixture stirred for 10 min. BocNHTs (1.95 g, 7.20 mmol) was added in one portion, and the mixture warmed to rt over 16 h. The mixture was concentrated, then redissolved in a minimal volume of CH₂Cl₂, and then filtered through a pad of silica, eluting with CH₂Cl₂. This organic phase was then washed successively with H₂O₂ (8 mL of a 15% v/v aq. solution), Na₂SO₃ (8 mL, sat., aq.) and H₂O (8 mL), then dried (Na₂SO₄), filtered and concentrated to afford the crude carbamate (2.34 g, 4.84 mmol, ~74%) as a colorless oil, which was used immediately to prevent spontaneous cyclisation to 1,3-ditosyltetrahydropyrimidine-2(1H)-one on standing and in solution.

To a rapidly stirring solution of this crude sulfonamide (200 mg, 0.414 mmol) in PhMe (4.1 mL) was added tetrabutylammonium hydrogensulfate (14.1 mg, 41.4 µmol) followed by 2,3-dibromopropene (108 mg, 0.539 mmol). NaOH (4.1 mL of a 25% w/v aq. solution) was added, and the mixture was stirred for 15 min, until starting material was consumed by tlc; then the layers were separated and extracted with Et₂O (2 × 5 mL). The combined organic fractions were dried (Na₂SO₄), filtered and concentrated in vacuo,* then redissolved in CH₂Cl₂ (3 mL) and cooled to 0 °C. TFA (1 mL) was added, and the reaction was stirred for 3 h, then diluted with H₂O (5 mL) and CH₂Cl₂ (3 mL) and the layers separated. The organic phase was dried as a colorless oil (663 mg, 54%); Rf 0.38 (petroleum ether / EtOAc (7:3)): ¹H NMR (400 MHz, CDCl₃) δₚ 7.76 (2H, d, J = 8.0 Hz, TsH), 7.72 (2H, d, J = 8.0 Hz, TsH), 7.35 (2H, d, J = 8.0 Hz, TsH), 7.32 (2H, d, J = 8.0 Hz, TsH), 5.84 (1H, d, J = 2.0 Hz, H₅), 5.62 (1H, d, J = 2.0 Hz, H₅'), 4.07 (2H, s, H₃), 3.49-3.46 (2H, m, H1), 3.41-3.37 (2H, m, H2), 2.46 (3H, s, TsCH₃), 2.44 (3H, s, TsCH₃), 2.24 (2H, t, J = 7.0 Hz, H₈), 1.52-1.43 (2H, m, H9), 1.36-1.23 (6H, m, H10, H11, H12), 0.89 (3H, t, J = 7.0 Hz, H13); ¹³C NMR (101 MHz, CDCl₃) δc 144.7, 143.9, 136.1, 134.1, 129.8, 129.8, 127.8, 127.6, 127.4, 120.5, 72.8, 70.5, 56.6, 50.6, 45.9, 31.3, 28.8, 28.5, 22.6, 21.7, 21.6, 18.4, 14.1; Data as reported previously.[¹⁶]

Preparation and use of N-(2-bromoallyl)-4-methyl-N-(3-((4-methylphenyl)sulfonamido)propyl) benzenesulfonamide, 9j

\[
\begin{align*}
\text{NH}_2 & \quad \text{TsCl, Et}_3\text{N} \\
\text{OH} & \quad \text{OH} \\
\text{NHTs} & \quad \text{PPh}_3, \text{DIAD, TsBocNH} \\
\text{Br} & \quad \text{Br} \\
\text{NTsBoc} & \quad \text{TBAHS} \quad \text{NaOH} \\
\text{TS} & \quad \text{Br} \\
\text{NTsBoc} & \quad \text{TFA} \\
\text{NHTs} & \quad \text{Br} \\
\end{align*}
\]

To a solution of PPh₃ (2.06 g, 7.85 mmol) in THF (30 mL) at 0 °C was added DIAD (1.35 mL, 6.87 mmol) steadily, and the mixture stirred for 15 min. A solution of crude tosylated product (1.50 g, 6.54 mmol) in THF (30 mL) was added dropwise, then the mixture stirred for 10 min. BocNHTs (1.95 g, 7.20 mmol) was added in one portion, and the mixture warmed to rt over 16 h. The mixture was concentrated, then redissolved in a minimal volume of CH₂Cl₂, and then filtered through a pad of silica, eluting with CH₂Cl₂. This organic phase was then washed successively with H₂O₂ (8 mL of a 15% v/v aq. solution), Na₂SO₃ (8 mL, sat., aq.) and H₂O (8 mL), then dried (Na₂SO₄), filtered and concentrated to afford the crude carbamate (2.34 g, 4.84 mmol, ~74%) as a colorless oil, which was used immediately to prevent spontaneous cyclisation to 1,3-ditosyltetrahydropyrimidine-2(1H)-one on standing and in solution.

To a rapidly stirring solution of this crude sulfonamide (200 mg, 0.414 mmol) in PhMe (4.1 mL) was added tetrabutylammonium hydrogensulfate (14.1 mg, 41.4 µmol) followed by 2,3-dibromopropene (108 mg, 0.539 mmol). NaOH (4.1 mL of a 25% w/v aq. solution) was added, and the mixture was stirred for 15 min, until starting material was consumed by tlc; then the layers were separated and extracted with Et₂O (2 × 5 mL). The combined organic fractions were dried (Na₂SO₄), filtered and concentrated in vacuo,* then redissolved in CH₂Cl₂ (3 mL) and cooled to 0 °C. TFA (1 mL) was added, and the reaction was stirred for 3 h, then diluted with H₂O (5 mL) and CH₂Cl₂ (3 mL) and the layers separated. The organic phase was dried...
(Na₂SO₄), filtered and concentrated in vacuo*, and the deprotected sulfonamide (68 mg, 0.135 mmol) was used immediately in the ynamide formation step (~21% yield over four steps).

*A water bath temperature of <20 °C was required during rotovap concentration to prevent decomposition. The intermediate must be used immediately or stored below –20 °C.

To a mixture of crude sulfonamide (68 mg, 0.136 mmol), K₃PO₄ (58 mg, 0.271 mmol), 1,10-phenanthroline (20 mg, 0.109 mmol), CuSO₄•5H₂O (14 mg, 0.821 mmol) and 1-bromo-1-octyne (34 mg, 0.271 mmol) was added anhydrous PhMe (0.70 mL) and the mixture heated to 85 °C for 16 h. The mixture was cooled to rt and passed through cotton wool, eluting with Et₂O, then the organic fraction was concentrated in vacuo.

Purification by flash chromatography (petroleum ether / EtOAc, 9:1) afforded the ynamide 3m as a colorless oil (42 mg, 0.080 mmol, 59%); Rf 0.38 (petroleum ether / EtOAc (7:3)); ¹H NMR (400 MHz, CDCl₃) δH 7.76 (2H, d, J = 8.0 Hz, TsH), 7.72 (2H, d, J = 8.0 Hz, TsH), 7.35 (2H, d, J = 8.0 Hz, TsH), 7.32 (2H, d, J = 8.0 Hz, TsH), 5.84 (1H, d, J = 2.0 Hz, H5), 5.62 (1H, d, J = 2.0 Hz, H5), 4.07 (2H, s, H3), 3.49-3.46 (2H, m, H1), 3.41-3.37 (2H, m, H2), 2.46 (3H, s, TsCH₂), 2.44 (3H, s, TsCH₂), 2.24 (2H, t, J = 7.0 Hz, H8), 1.52-1.43 (2H, m, H9), 1.36-1.23 (6H, m, H10, H11, H12), 0.89 (3H, t, J = 7.2 Hz, H13); ¹³C NMR (101 MHz, CDCl₃) δC 144.7, 143.9, 136.1, 134.1, 129.8, 129.8, 127.8, 127.6, 127.4, 120.5, 72.8, 70.5, 56.6, 50.6, 45.9, 31.3, 28.8, 28.5, 22.6, 21.7, 21.6, 18.4, 14.1. Data as reported previously.[16]

Synthesis of bromoalkynes 13a-e

METHOD A: n-BuLi; Br₂

METHOD B: NBS, cat. AgNO₃

1-Bromo-oct-1-yn, 13a

Preparation by General Procedure C: Using 1-octyne (6.69 mL, 45.4 mmol). Concentration in vacuo (care due to product volatility!) gave 13a as a pale yellow oil (8.32 g, 44.0 mmol, 96%), which was used without further purification; Rf 0.70 (petroleum ether / EtOAc, 10:1); ¹H NMR (400 MHz, CDCl₃) δH 2.19 (2H, t, J = 7.2 Hz, H3), 1.50 (2H, app quin, J = 7.2 Hz, H4), 1.43-1.20 (6H, m, H5-H7), 0.89 (3H, t, J = 7.2 Hz, H8); ¹³C NMR (101 MHz, CDCl₃) δC 80.4, 37.4, 31.3, 28.5, 28.3, 22.5, 19.7, 14.0. Data in accordance with literature values.[17]
Preparation by General Procedure D: Synthesised from oct-1-yne (15.0 mL, 102 mmol). The resulting crude material was purified by column chromatography (petroleum ether) to give 13a as a colorless oil (18.4 g, 97.5 mmol, 96%); Data in accordance with the above.

(Bromoethynyl)benzene, 13b

Preparation by General Procedure C: Using phenylacetylene (5.0 mL, 45.5 mmol). Concentration in vacuo gave 13b as a pale yellow oil (8.45 g, 45.5 mmol, 99%), which was used without further purification; \( R_f = 0.68 \) (5:1, petroleum ether:EtOAc); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.48 (2H, dd, \( J = 7.7, 1.9 \) Hz, ArH), 7.38-7.29 (3H, m, ArH); \(^13\)C NMR (101 MHz, CDCl\(_3\)) \( \delta \) C 132.0, 128.6, 128.3, 122.7, 80.0, 49.7. Data in accordance with literature values.[18]

Preparation by General Procedure D: Synthesised from phenylacetylene (5.00 mL, 45.5 mmol). The crude material was purified by column chromatography (petroleum ether) to give 13b as a yellow oil (5.99 g, 33.1 mmol, 73%). Data in accordance with the above.

((5-Bromopent-4-yn-1-yl)oxy)(tert-butyl)dimethylsilane, 13c

To a stirred suspension of NaH (60% in mineral oil, 1.43 g, 35.5 mmol, 1.08 equiv.) in THF (50 mL) at rt was added 4-pentyn-1-ol (2.77 g, 32.9 mmol, 1 equiv.), and this was left to stir for 30 min. Then TBSCl (5.38 g, 35.7 mmol, 1.08 eq.) was added portionwise. Following completion of the reaction as judged by tlc, the reaction was quenched with K\(_2\)CO\(_3\) (sat., aq.), then diluted with water and extracted with ether. The combined organic layers were dried (MgSO\(_4\)) and concentrated to afford tert-butylidimethyl(pent-4-yloxy)silane as a colorless oil (5.84 g, 29.4 mmol, 89%); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) H 3.70 (2H, t, \( J = 6.0 \) Hz, H1), 2.28 (2H, dt, \( J = 7.1, 2.3 \) Hz, H3), 1.94 (1H, \( J = 2.3 \) Hz, H5), 1.73 (2H, m, H2), 0.90 (9H, s, SiMe\(_2\)-t-Bu), 0.06 (6H, s, SiMe\(_2\)-t-Bu). Data in agreement with literature values.[19]

This product was converted to the bromalkyne 13c using General Procedure C: Using 7.86 g (39.6 mmol) of the alkyne, 13c was obtained as a brown liquid (10.0 g, 36.0 mmol, 91%); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) H 3.68 (2H, t, \( J = 6.0 \) Hz, H1), 2.29 (2H, t, \( J = 7.0 \) Hz, H3), 2.29 (2H, tt, \( J = 7.0, 6.0 \) Hz, H2), 0.89 (9H, s, SiMe\(_2\)-t-Bu), 0.05 (6H, s, SiMe\(_2\)-t-Bu); \(^13\)C NMR (101 MHz, CDCl\(_3\)) \( \delta \) C 79.9, 61.3, 37.7, 31.2, 25.9, 18.3, 16.1, 5.4. Data in agreement with literature values.[19]

This bromoalkyne could also be prepared using General Procedure D, according to the procedure of Sabitha.[19]
(Bromoethynyl)trimethylsilane, 13d

Preparation by General Procedure C: Using TMS acetylene (2.98 g, 30.2 mmol). This gave 13d as a pale yellow liquid (5.32 g, 30.0 mmol, 99%); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 0.18 (9H, s, TMS); \(^1\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) C 87.0, 61.4, 0.3. Data in agreement with literature values.\(^{[20]}\)

Preparation by General Procedure D: Using TMS acetylene (5.00 mL, 35.4 mmol). Purification by flash chromatography (petroleum ether) have 13d as a yellow oil (4.83 g, 27.3 mmol, 77%).

(Bromoethynyl)triisopropylsilane, 13e

Preparation by General Procedure C: Using TIPS acetylene (0.81 g, 4.46 mmol). This gave 13e as a light brown liquid (1.06 g, 4.06 mmol, 91%); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) H 1.09 (21H, s, TIPS); \(^1\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) C 83.4, 61.7, 18.4, 11.2. Data in agreement with literature values.\(^{[21]}\)

Bromoalkyne 13f was prepared according to the following scheme:

\[
\text{(S)-4,8-Dimethylnon-7-en-1-yne, S8}
\]

To a mixture of [Ph\(_3\)PCHBr\(_2\)]Br (5.71 g, 11.1 mmol) in THF (50 mL) at rt was added KO\(_t\)-Bu (1.18 g, 10.5 mmol) in a single portion, and the mixture was stirred for 2 min. (S)-Citronellal (855 mg, 5.54 mmol) was added and the mixture was stirred for 10 min, before addition of further KO\(_t\)-Bu (3.11 g, 27.7 mmol). After 10 min, the reaction was quenched with brine (50 mL), concentrated in vacuo* to remove the THF, then extracted with Et\(_2\)O (50 mL). The mixture was concentrated in vacuo* and the product was triturated with petroleum ether (30 mL), again concentrated in vacuo*, and then purified by column chromatography (petroleum ether eluent) to obtain the alkyne S8 as a volatile colorless oil (557 mg, 67%); \(R_f\) 0.87 (petroleum ether); IR (thin film) \(v_{\text{max}}\) / cm\(^{-1}\) 3311, 2995, 2918, 2063, 1455, 1378, 1110, 911, 736, 630; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) H 5.11 (1H, br t, \(J = 7.0\) Hz, H7), 2.19 (1H, ddd, \(J = 16.5, 5.5, 2.5\) Hz, H3), 2.09 (1H, ddd, \(J = 16.5, 8.0, 2.5\) Hz, H3'), 2.04-1.97 (2H, m, H6), 1.96 (1H, t, \(J = 2.5\) Hz, H1), 1.75-1.64 (1H, m, H4), 1.69 (3H,
s, CH₃), 1.62 (3H, s, CH₃), 1.51-1.39 (1H, m, H5), 1.30-1.20 (1H, m, H5'), 1.00 (3H, d, J = 6.5 Hz, H10); ¹³C NMR (101 MHz, CDCl₃) δC 83.3, 79.0, 73.3, 69.4, 66.0, 33.2, 32.5, 29.2, 26.6, 25.7, 23.3, 19.6, 15.4; HRMS (ES⁺) calc. for C₁₁H₂₁O₂ [M+H]⁺ 185.1536, found 185.1531.

*NB Due to the volatility of the alkyne, careful concentration in vacuo must be observed.

(3R,6S)-2,6-Dimethylnon-8-yne-2,3-diol, 15

![Diagram of compound 15]

To a solution of (S)-4,8-dimethylnon-7-en-1-ynyl S₈ (294 mg, 1.96 mmol) in t-BuOH / H₂O (18 mL (1:1)) was added methanesulfonamide (222 mg, 1.96 mmol) followed by AD-mix-β (2.66 g). The mixture was stirred at rt for 72 h then Et₂O (20 mL) was added, and the layers separated. The organic fraction was washed with H₂O (20 mL), dried (Na₂SO₄), filtered and concentrated to afford the diol 15 as a colorless oil (314 mg, 87%); Rf 0.37 (Et₂O); IR (thin film) νmax / cm⁻¹ 3452 (br), 3309, 2957, 2112, 1460, 1380, 1160, 1065, 963; ¹H NMR (400 MHz, CDCl₃) δH 3.35-3.29 (1H, m, H7), 2.48-2.41 (1H, br d, J = 4.0 Hz, OH), 2.25-2.22 (1H, br s, OH), 2.19 (1H, ddd, J = 16.5, 5.5, 2.5 Hz, H6), 2.09 (1H, ddd, J = 16.5, 6.5, 2.5 Hz, H6'), 1.96 (1H, t, J = 2.5 Hz, H1), 1.75-1.64 (2H, m, H3), 1.55-1.45 (1H, m, H4) 1.32-1.23 (2H, m, H5), 1.20 (3H, s, H9), 1.15 (3H, s, H9'), 1.01 (3H, d, J = 6.5 Hz, H10); ¹³C NMR (101 MHz, CDCl₃) δC 83.3, 79.0, 73.3, 69.4, 66.0, 33.2, 32.5, 29.2, 26.6, 25.7, 23.3, 19.6, 15.4; HRMS (ES⁺) calc. for C₁₁H₂₁O₂ [M+H]⁺ 185.1536, found 185.1531; [α]D²⁰ +10.2 (c 0.5, CHCl₃).

(R)-2,2,4,4-Tetramethyl-5-((S)-3-methylhex-5-yn-1-yl)-1,3-dioxolane, S₉

![Diagram of compound S₉]

To a solution of diol 15 (352 mg, 1.57 mmol) in aceton (6.3 mL) was added dimethoxypropane (2.75 mL, 22.2 mmol) followed by βTSA.H₂O (12.9 mg, 0.0676 mmol), and the mixture was stirred for 1 h. The reaction was quenched with NaHCO₃ (10 mL, sat., aq.) and extracted with Et₂O (2 × 10 mL). The combined organic extracts were dried (Na₂SO₄), filtered and concentrated to afford the crude acetonide as a colorless oil. Purification by silica chromatography (petroleum ether / Et₂O, 9:1) gave the purified acetonide S₉ as a colorless oil (369 mg, 86%); Rf 0.41 (petroleum ether/Et₂O (9:1)); IR (thin film) νmax / cm⁻¹ 3311, 2979, 2912, 2117, 1458, 1369, 1273, 1217, 1199, 1116, 998, 854, 629; ¹H NMR (400 MHz, CDCl₃) δH 3.66 (1H, dd, J = 8.5, 4.5 Hz, H7), 2.21 (1H, ddd, J = 16.5, 5.5, 3.0 Hz, H6), 2.10 (1H, ddd, J = 16.5, 7.0, 3.0 Hz, H6'), 1.97
(1H, t, J = 2.5 Hz, H1), 1.78-1.61 (2H, m, H3), 1.56-1.43 (1H, m, H4) 1.42 (3H, s, CH3), 1.33 (3H, s, CH3), 1.25 (3H, s, CH3), 1.10 (3H, s, CH3), 1.02 (3H, d, J = 7.0 Hz, H10; 13C NMR (101 MHz, CDCl3) δ 106.6, 83.7, 83.2, 80.3, 69.4, 33.2, 32.6, 28.7, 27.0, 26.3, 25.9, 19.3; HRMS (ES+) calc. for C14H25O2 [M+H]+ 225.1855, found 185.1849; [α]D20 −16.2 (c 1, CHCl3).

(R)-5-((S)-6-Bromo-3-methylhex-5-yn-1-yl)-2,2,4,4-tetramethyl-1,3-dioxolane, 13f

\[
\begin{align*}
\text{Br} & \quad 1 \\
\text{O} & \\
\text{Br} & \quad 10
\end{align*}
\]

To a solution of terminal acetylene S9 (306 mg, 1.37 mmol) in acetone (2.7 mL) was added AgNO3 (23.3 mg, 0.137 mmol), and the mixture was stirred for 5 min before addition of N-bromosuccinimide (255 mg, 1.44 mmol). After 2 h, the mixture was diluted with Et2O (10 mL) and filtered through celite, eluting with Et2O (10 mL), then the mixture was concentrated. Rapid purification by flash chromatography (petroleum ether / Et2O, 9:1 eluent) gave the bromoalkyne 13f as a colorless oil (369 mg, 86%), which was used immediately as the product underwent decomposition on standing and in the freezer at −20 °C; Rf 0.59 (petroleum ether/Et2O (4:1)); 1H NMR (400 MHz, CDCl3) δH 3.61 (1H, dd, J = 8.5, 4.0 Hz, H7), 2.18 (1H, dd, J = 16.5, 5.5 Hz, H6), 2.07 (1H, dd, J = 16.5, 7.0, H6′), 1.71-1.51 (2H, m, H3), 1.51-1.40 (1H, m, H4) 1.37 (3H, s, CH3), 1.29 (3H, s, CH3), 1.21 (3H, s, CH3), 1.05 (3H, s, CH3), 0.96 (3H, d, J = 7.0 Hz, H10).

Bromoalkyne 13g was prepared according to the following scheme:

\[
\begin{align*}
\text{PPPh3, CBr4} & \\
\text{S10} & \\
\text{LiHMDS} & \\
\text{13g}
\end{align*}
\]

3-(2,2-Dibromoethyl)-1-(phenylsulfonyl)indole, S10

To a solution of PPPh3 (8.57 g, 32.6 mmol) in CH2Cl2 (35 mL) at −20 °C was added CBr4 (5.41 g, 16.3 mmol) in a single portion. The mixture was stirred for 10 min, then cooled to −78 °C before dropwise addition of a solution of N-tosylindole-3-carboxaldehyde (1.63 g, 5.44 mmol) in CH2Cl2 (10 mL). Stirring was continued for 5 min, then the mixture was warmed to rt before addition of hexane (40 mL). The precipitate was filtered, concentrated in vacuo, redissolved in CHCl3 (20 mL) and reconcentrated, then purified via rapid
chromatography through a pad of silica (petroleum ether / EtOAc, 1:3) to afford the vinyl dibromide S10 as a pale yellow solid (2.03 g, 82%); mp 113–118 °C; $R_f$ 0.42 (petroleum ether/EtOAc (1:3)); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$H 8.30 (1H, d, $J = 1.0$ Hz, H15), 8.00 (1H, dt, $J = 8.5$, 1.0 Hz, H5), 7.80 (2H, dt, $J = 8.5$, 2.0 Hz, TsH), 7.55 (1H, d, $J = 0.5$ Hz, H2), 7.53 (1H, dt, $J = 7.5$, 1.0 Hz, H8), 7.37 (1H, ddd, $J = 8.5$, 7.5, 1.0 Hz, H7), 7.31-7.28 (1H, m, H6), 7.26-7.23 (2H, m, TsH), 2.35 (3H, s, TsC$_3$H$_3$); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$C 145.5, 135.0, 134.2, 130.1, 129.5, 127.0, 125.6, 125.1, 123.7, 118.9, 117.5, 113.8, 90.4, 21.8; LRMS (ESI$^+$) C$_{16}$H$_{11}$NO$_2$SBr$_2$ 441.0 (100, [M+H]$^+$). Data are in agreement with the literature.$^{[22]}$

3-(Bromoethynyl)-1-tosyl-1H-indole, 13g

To a solution of vinyl dibromide (900 mg, 1.98 mmol) in THF (15 mL) at $-78$ °C was added LHMDS (2.37 mL of a 1 M solution in THF, 2.37 mmol) dropwise and the mixture was stirred for 20 min, before being quenched with NH$_4$Cl (10 mL, sat., aq.). The product was extracted with EtOAc (2 $\times$ 10 mL), then the organic fractions were combined, dried (MgSO$_4$), filtered and concentrated, giving the bromoalkyne as a colorless oil (696 mg, 94%) which was used without further purification. IR (thin film) $\nu_{\text{max}}$ / cm$^{-1}$ 3033, 2954, 2201, 1597, 1446, 1375, 1175; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$H 7.97 (1H, dt, $J = 8.5$, 1.0 Hz, H5), 7.81-7.74 (3H, m, H2, H11), 7.64 (1H, app dq, $J = 8.0$, 0.5 Hz, H8), 7.36 (1H, ddd, $J = 8.5$, 7.0, 1.0 Hz, H7), 7.32-7.28 (1H, m, H6), 7.26-7.23 (2H, m, H12), 2.36 (3H, s, TsCH$_3$); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$C 145.6, 134.9, 134.1, 130.8, 130.2, 130.0, 127.1, 125.7, 124.0, 120.6, 113.7, 104.8, 71.6, 53.6, 21.8; HRMS (ES$^+$) calc. for C$_{17}$H$_{12}$BrNaO$_2$S$^+$ ([M+Na]$^+$) 395.9664, found 395.9674.

Bromoalkyne 13h was prepared according to the following scheme:

(R)-(4-(Bromo-2-methylbut-3-yn-1-yl)oxy)methyl)benzene, 13h

To a solution of methyl (R)-3-(benzyloxy)-2-methylpropanoate (1.00 g, 4.80 mmol) in CH$_2$Cl$_2$ (13 mL) at $-78$ °C was added dropwise a solution of DIBAL (4.80 mL of a 1 M solution in CH$_2$Cl$_2$, 4.80 mmol). The mixture was maintained at $-78$ °C for 1 h, then quenched carefully with MeOH at this temperature. Sodium potassium tartrate (10 mL, sat., aq.) was added, and the mixture was stirred at rt for 2 h. The layers were separated and the product was extracted with CH$_2$Cl$_2$ (2 $\times$ 10 mL). The organics extracts were combined,
dried (Na$_2$SO$_4$), filtered and concentrated in vacuo (20 °C) to obtain the crude aldehyde S11, which was used immediately to prevent racemisation (assumed quantitative). To a mixture of [Ph$_3$PCHBr$_2$]Br (4.95 g, 9.61 mmol) in THF (30 mL) at rt was added KOt-Bu (1.03 g, 9.18 mmol), and the mixture was stirred for 20 min. To the generated ylide was added crude (R)-3-(benzyloxy)-2-methylpropanal S11 (856 mg, 4.80 mmol). The mixture was stirred for 10 min at rt, then diluted with petroleum ether (100 mL), and the precipitate removed by filtration, washing with petroleum ether (100 mL). Following concentration, rapid purification through a pad of silica (petroleum ether / Et$_2$O, 19:1 eluent) gave the vinyl dibromide S12 as a colorless oil (615 mg), which was used directly in the subsequent step.

To a solution of crude vinyl dibromide S12 (524 mg, 1.57 mmol) in THF (7 mL) –78 °C was added KHMDS (3.34 mL of a 0.47 M solution in toluene, 1.57 mmol) dropwise. The mixture was stirred at –78 °C for 30 min, then warmed to –20 °C for 30 min, then quenched at this temperature with NH$_4$Cl (5 mL, sat., aq.). The product was extracted with Et$_2$O (3 × 10 mL), washed with brine (10 mL) then dried (MgSO$_4$), filtered and concentrated in vacuo.* The product was purified by flash chromatography (petroleum ether / Et$_2$O, 19:1 eluent) to afford the 13h as a colorless oil (354 mg, 89%).

* NB Water bath temperature of <20 °C was used to minimise decomposition. Product was used immediately as underwent significant decomposition at ambient temperature and in solution.

**R**$^f$ 0.61 (petroleum ether/Et$_2$O (9:1)); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$H 7.45-7.28 (5H, m, PhH), 4.57 (2H, br s, PhCH$_2$), 3.52 (1H, dd, J = 9.0, 6.5 Hz, OCH$_A$H$_B$), 3.38 (1H, dd, J = 9.0, 7.0 Hz, OCH$_A$H$_B$), 2.78 (1H, sxt, J = 7.0 Hz, CHMe), 1.23 (3H, d, J = 7.0 Hz, CH$_3$); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$c: 138.2, 128.5, 127.7, 127.7, 82.2, 73.1, 73.6, 39.4, 28.0, 17.5; LRMS (ESI$^+$) C$_{12}$H$_{13}$BrNaO [M+Na]$^+$ 275.0; $[^{[\alpha]}]_D^{20}$–8.5 (c 1, CHCl$_3$).

**Bromoenynamide formation:** Ynamide formation was generally achieved using either the Hsung (or Evano) coupling of bromoalkynes (or dibromoalkenes) with the relevant amides, see General Procedure E. The characterization of ynamides 3a-m has been reported in our earlier communications.$^{[16, 23]}$ For ynamides 3n-q, problems encountered using these copper-catalyzed methods necessitated ynamide synthesis using the Witulski method of alkynyl iodonium triflate salts,$^{[24]}$ characterization data for these compounds has also been described previously.$^{[16, 23]}$

**4. Stannane Synthesis**

All stannanes employed in this work are known compounds. These were prepared according to the following procedures:

**Tributylpropenylstannane (19a):** Prepared according to the procedure of Moloney et al.$^{[25]}$

**Tributylstyrenylstannane (19b):** Prepared as 19a.
Tributylvinylstannane (19c): Prepared according to the procedure of Seyferth and Stone.  

\[
\text{Ph}^\gamma\text{CH} \quad \text{Bu}_3\text{SnCl} \quad \text{t-BuLi, THF, } -78 \, ^\circ \text{C to } 0 \, ^\circ \text{C; Bu}_3\text{SnCl} \quad \text{Ph}^\gamma\text{CHSnBu}_3 \quad 19b
\]

Tributyl(3,4-dihydro-2H-pyran-6-yl)stannane (19e): Prepared according to the procedure of Quayle et al.  

\[
\text{O} \quad \text{MgBr, Bu}_3\text{SnCl, THF, } 65 \, ^\circ \text{C} \quad \text{Bu}_3\text{SnCl, -78 } ^\circ \text{C; Bu}_3\text{SnCl, -78 } ^\circ \text{C} \quad \text{O}^\gamma\text{CH} \quad \text{Bu}_3\text{SnBu}_3 \quad 19e
\]
VT **H NMR experiment (Main paper, Figure 2) to determine reaction initiation temperature and the evolution of product and intermediate

**Procedure:** To an NMR tube containing PdCl$_2$(PPh$_3$)$_2$ (10 mol%) under Ar was added a degassed (Ar bubbling) solution of stannane 19a (30 mg, 0.091 mmol) and bromoenynamide 3a (23.5 mg, 0.057 mmol) in d$_8$-toluene (0.8 mL). The NMR tube was placed in a 500 MHz spectrometer at rt, then gradually heated to 95 °C in 5 °C increments until initiation of reaction was observed. The reaction was held at 95 °C for ~45 min until complete consumption of starting material and intermediate.
Isolation of \((E)-2-((E)-\text{dec-2-en-4-ylidene})-3\text{-methylene-1-tosylpyrrolidine (20)}:

Isolation of \((E)-2-((E)-\text{dec-2-en-4-ylidene})-3\text{-methylene-1-tosylpyrrolidine (20)}: \) To an NMR tube containing PdCl\(_2\)(PPh\(_3\))\(_2\) (3.4 mg, 0.0048 mmol, 10 mol%) under Ar was added a degassed (Ar bubbling, 15 min) solution of the bromoenynamide \(3a\) (20 mg, 0.048 mmol) and stannane \(19a\) (26 mg, 0.078 mmol) in d\(_8\)-toluene (0.8 mL). Alongside this, an equivalent sample was made up containing bromoenynamide and stannane in d\(_8\)-toluene, but no catalyst. A room temperature \(^1\)H NMR spectrum of both samples was taken to acquire a spectrum at \(t=0\); then, the control sample (no catalyst) was heated to 90 °C for the purpose of retuning and shimming of the probe and sample. The reaction sample was then inserted into the pre-heated spectrometer, and monitored by \(^1\)H NMR with acquisitions at 2 minute intervals. The reaction reached a peak of intermediate production at 12-13 minutes. After cooling to rt (i.e. reaction was halted), the sample was concentrated, and purified by flash chromatography (2% EtOAc in petroleum ether). This afforded 3.1 mg of a fraction containing \(20, 3a, 4a,\) and the amide \(S13\) in a \(1 : 0.23 : 0.8 : 0.5\) ratio. The amide \(S13\) is believed to arise from partial hydrolysis of the starting material in the course of exposure to SiO\(_2\) during purification by slow column chromatography. This procedure was performed three times with equivalent results.

The stereochemistry of \(20\) was proven by nOe enhancement between protons H2 and H3; the assignment of structure was made on the basis of \(^1\)H NMR chemical shifts for these protons and the associated methyl group, and by analogy to trienes prepared and isolated in earlier work from our group.

This triene was then subjected to a further VT NMR experiment, which confirmed complete conversion to the dienamide \(4a\), in the absence of catalyst. Notably, consumption of this intermediate was also observed in all standard VT NMR reactions (i.e. in the presence of the catalyst), according to our optimization experiments and as shown in Figure 2 of the paper.
6. Ynamide carbopalladation / Stille coupling / electrocyclization cascades

These were carried out using General Procedure F.

7-Hexyl-5-methyl-1-tosyl-2,3,4,5-tetrahydro-1H-indole, 4a

![Structure of 4a](image)

Synthesised from ynamide 3a (100 mg, 0.243 mmol), stannane 19a (129 mg, 0.388 mmol), and PdCl₂(PPh₃)₉ (17.0 mg, 0.024 mmol, 10 mol%) using General Procedure F, to afford 4a as a yellow oil (84.0 mg, 0.225 mmol, 92%); Rf 0.30 (petroleum ether / ether, 3:1); ¹H NMR (500 MHz, CDCl₃) δH 7.68 (2H, d, J = 8.2 Hz, TsH), 7.27 (2H, d, J = 8.0 Hz, TsH), 5.38 (1H, s, H6), 3.87 (1H, ddd, J = 13.0, 8.0, 3.3 Hz, H2), 3.66 (1H, dt, J = 13.1, 9.4 Hz, H2), 2.65-2.59 (1H, m, H5), 2.44 (3H, s, TsMe), 2.42-2.32 (2H, m, H4), 1.93 (1H, dd, J = 17.4, 7.8 Hz, H3), 1.74 (1H, dd, J = 17.5, 2.3 Hz, H3), 1.69-1.24 (10H, m, H1''-5''), 1.07 (3H, d, J = 6.5 Hz, H1'), 0.88 (3H, t, J = 6.6 Hz, H6''); ¹³C NMR δC; 134.7, 138.5, 134.1, 133.1, 129.1, 128.4, 128.2, 51.5, 32.0, 31.8, 31.7, 30.5, 29.5, 28.9, 28.8, 22.6, 21.6, 20.2, 14.1; HRMS (ES⁺) calc. for C₂₂H₂₄NNaO₂S [M+Na]^+ 396.1968; found 396.1961. Also prepared by General Procedure F using ynamide 3a (50 mg, 0.12 mmol), stannane 19a (63 mg, 0.19 mmol), and PdCl₂(PPh₃)₉ (~1.0 mg, 0.0012 mmol, 1 mol%), with heating for 18 h. Purification via flash chromatography (petroleum ether + 1% NEt₃ → petroleum ether / EtOAc (10:1) + 1% NEt₃) afforded amidodiene 4a as a pale yellow oil (40.7 mg, 0.109 mmol, 90%).

7-(3-(tert-Butyldimethylsilyloxy)propyl)-5-methyl-1-tosyl-2,3,4,5-tetrahydro-1H-indole, 4b

![Structure of 4b](image)

Synthesised from ynamide 3c (100 mg, 0.20 mmol), stannane 19a (106 mg, 0.32 mmol) and PdCl₂(PPh₃)₉ (14.0 mg, 0.020 mmol, 10 mol%) using General Procedure F to afford 4b as a yellow oil (84.0 mg, 0.182 mmol, 91%); Rf 0.38 (petroleum ether / EtOAc, 3:1); IR (thin film) νmax / cm⁻¹ 2957, 2738, 1597, 1493, 1353, 1254, 1165; ¹H NMR (400 MHz, CDCl₃) δH 7.66 (2H, d, J = 8.3 Hz, TsH), 7.26 (2H, d, J = 8.3 Hz, TsH), 5.39 (1H, s, H6), 3.90-3.84 (1H, m, H2), 3.70-3.63 (1H, m, H2), 3.67 (2H, t, J = 7.4 Hz, H3''), 3.62 (2H, t, J = 7.4 Hz, H1''), 2.71-2.63 (1H, m, H5), 2.43 (3H, s, TsMe), 2.42-2.35 (2H, m, H4), 1.94 (1H, dd, J = 17.5, 8.0 Hz, H3), 1.83-1.50 (3H, m, H2'', H3), 1.06 (3H, d, J = 7.1 Hz, H1''), 0.90 (9H, s, OSiMe₂-t-Bu), 0.05 (6H, s, OSiMe₂-t-Bu); ¹³C NMR (101 MHz, CDCl₃) δC 143.7, 138.3, 133.3, 133.0, 132.8, 129.2, 128.7, 128.4, 62.9, 51.5, 31.8, 30.5, 29.5, 28.2, 26.0, 21.6, 20.2, 18.4, 13.5, -5.2; HRMS (ES⁺) calc. for C₂₅H₃₀NNaO₂SSi [M+Na]^+ 484.2312, found 484.2304.
Also prepared by General Procedure F using ynamide 3c (50 mg, 0.10 mmol), stannane 19a (53 mg, 0.16 mmol) and PdCl₂(PPh₃)₂ (~0.9 mg, 0.001 mmol, 1 mol%), with heating for 18 h. Purification via column chromatography (petroleum ether + 1% NEt₃ → petroleum ether / EtOAc (10:1) + 1% NEt₃) afforded amidodiene 4b as a pale yellow oil (34 mg, 0.076 mmol, 76%).

5-Methyl-7-phenyl-1-tosyl-2,3,4,5-tetrahydro-1H-indole, 4c

Synthesised from ynamide 3b (50 mg, 0.124 mmol), stannane 19a (63 mg, 0.198 mmol), and PdCl₂(PPh₃)₂ (0.8 mg, 0.0012 mmol, 1 mol%) with heating for 18 h. Purification via column chromatography (petroleum ether / ether, 3:1) afforded amidodiene 4c as a pale brown oil (21.9 mg, 0.081 mmol, 65%);

7-Hexyl-5-phenyl-1-tosyl-2,3,4,5-tetrahydro-1H-indole, 4d

Synthesised from ynamide 3a (100 mg, 0.24 mmol), stannane 19b (153 mg, 0.39 mmol), and PdCl₂(PPh₃)₂ (17.0 mg, 0.024 mmol, 10 mol%) using General Procedure F to afford 4d as a yellow oil (81.6 mg, 0.18 mmol, 77%); Rf 0.23 (petroleum ether / ether, 3:1); ¹H NMR (500 MHz, CDCl₃) δH 7.69 (2H, d, J = 8.2 Hz, TsH), 7.39-7.28 (5H, m, ArH), 7.22 (2H, d, J = 8.2 Hz, TsH), 7.52 (1H, s, H6), 3.96-3.88 (2H, m, H2), 3.64-3.57 (1H, m, H5), 2.77-2.70 (1H, m, H1'), 2.50-2.40 (1H, m, H1'), 2.44 (3H, s, TsCH₃), 2.37-2.16 (2H, m, H4), 1.69-1.59 (2H, m, H3), 1.57-1.27 (8H, m, H1'-H5'), 0.90 (3H, t, J = 7.0 Hz, H6'); HRMS (ES+) calc. for C₂₂H₂₃NNaO₂S [M+H]⁺ 388.1342, found 388.1332.
C$_2$H$_4$NO$_2$S [M+H]$^+$ 436.2305, found 436.2299. The data for this compound are as previously reported.\[16\]

7-Hexyl-1-tosyl-2,3,4,5-tetrahydro-1H-indole, 4e

![Chemical structure of 4e]

Synthesised from ynamide 3a (100 mg, 0.24 mmol), stannane 19c (123 mg, 0.39 mmol), and PdCl$_2$(PPh$_3$)$_2$ (17.0 mg, 0.024 mmol, 10 mol%) using General Procedure F to afford 4e as a yellow oil (63 mg, 0.175 mmol, 72%); $R_f$ 0.44 (petroleum ether / EtOAc, 3:1); IR (thin film) $\nu_{\text{max}}$/ cm$^{-1}$ = 2927, 1727, 1598, 1463, 1378, 1288, 1163, 1073; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$H 7.67 (2H, d, $J$ = 8.0 Hz, TsH), 7.26 (2H, d, $J$ = 8.0 Hz, TsH), 5.61 (1H, t, $J$ = 4.5 Hz, H6), 3.76 (2H, t, $J$ = 7.5 Hz, H2), 2.56-2.49 (2H, m, H5), 2.44 (3H, s, TsMe), 2.16-2.06 (2H, m, H6), 1.99-1.91 (2H, m, H4), 1.63 (2H, t, $J$ = 7.5 Hz, H3), 1.50-1.39 (2H, s, TsMe), 1.45-1.25 (2H, m, H2'); 1.36-1.25 (6H, m, H3'–5'); 0.88 (3H, t, $J$ = 7.0 Hz, H6'); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$C 143.7, 138.7, 135.1, 132.9, 132.4, 129.1, 128.3, 120.8, 51.2, 32.1, 31.8, 30.5, 28.9, 28.8, 23.7, 23.0, 21.6, 14.1, 13.6; HRMS (ES+) calc. for C$_{21}$H$_{29}$NNaO$_2$S [M+Na]$^+$ 382.1811, found 382.1807.

The data for this compound are as previously reported.[16]

7-Hexyl-1-tosyl-2,3,4,5-tetrahydro-1H-indole, 4f

![Chemical structure of 4f]

Synthesised from ynamide 3a (100 mg, 0.24 mmol), stannane 19d (151 mg, 0.39 mmol), and PdCl$_2$(PPh$_3$)$_2$ (17.0 mg, 0.024 mmol, 10 mol%) using General Procedure F to afford 4f as a yellow oil (93 mg, 0.215 mmol, 89%); $R_f$ 0.52 (petroleum ether / EtOAc, 3:1); IR (thin film) $\nu_{\text{max}}$/ cm$^{-1}$ = 2926, 1597, 1464, 1352, 1249, 1164, 838; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$H 7.69 (2H, d, $J$ = 8.2 Hz, TsH), 7.27 (2H, d, $J$ = 8.2 Hz, TsH), 5.45 (1H, s, H6), 3.86 (1H, ddd, $J$ = 12.9, 7.9, 2.4 Hz, H2), 3.63 (1H, ddd, $J$ = 12.9, 10.5, 9.1 Hz, H2), 2.81-2.75 (1H, m, H5), 2.45 (3H, s, TsMe), 2.32-2.22 (1H, m, H3), 2.01-1.73 (2H, m, H4), 1.79 (1H, dd, $J$ = 16.6, 8.8 Hz, H1'), 1.69-1.23 (9H, m, H1'–5'), 0.93 (3H, t, $J$ = 7.3 Hz, H6'), 0.05 (9H, s, TMS); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$C 143.7, 138.6, 134.8, 133.4, 132.4, 129.1, 128.3, 122.5, 51.5, 32.5, 31.8, 30.5, 29.2, 28.8, 24.5, 22.7, 22.7, 21.6, 14.1, -3.2; HRMS (ES+) calc. for C$_{24}$H$_{37}$NNaO$_2$Si [M+Na]$^+$ 454.2206, found 454.2198.
7-(3-(tert-Butyldimethylsilyloxy)propyl)-5-phenyl-1-tosyl-2,3,4,5-tetrahydro-1H-indole, 4g

Synthesised from ynamide 3c (100 mg, 0.20 mmol), stannane 19b (106 mg, 0.32 mmol), and PdCl₂(PPh₃)₂ (14.0 mg, 0.020 mmol, 10 mol%) using General Procedure F to afford 4g as a pale yellow oil (92 mg, 0.175 mmol, 89%); Rf 0.39 (petroleum ether / EtOAc, 3:1); IR (thin film) νₒ max/cm⁻¹ = 2929, 2857, 1598, 1493, 1352, 1251, 1164; ¹H NMR (400 MHz, CDCl₃) δH 7.68 (2H, d, J = 8.1 Hz, TsH), 7.38-7.25 (5H, m, ArH), 5.65 (1H, s, H6), 3.95-3.55 (2H, m, H2), 3.68 (2H, t, J = 6.7 Hz, H3'), 3.60 (2H, m, J = 7.7 Hz, H1'), 2.77 (1H, m, H5), 2.59-2.46 (2H, m, H4), 2.44 (3H, s, TsMe), 2.36-2.17 (2H, m, H3), 1.85-1.61 (2H, m, H2'), 0.91 (9H, s, OSiMe₂t-Bu), 0.08 (6H, s, OSi₂t-Bu); ¹³C NMR (101 MHz, CDCl₃) δC 144.9, 143.8, 138.6, 134.6, 133.0, 132.2, 129.2, 128.5, 128.4, 127.5, 126.5, 125.8, 125.0, 63.0, 51.5, 41.1, 32.4, 31.9, 30.4, 28.3, 26.0, 21.7, 18.4, -5.2; HRMS (ES⁺) calc. for C₃₀H₄₁NNaO₃Si [M+Na]⁺ 546.2469, found 546.2472.

9-Hexyl-8-tosyl-2,3,4,4a,5,6,7,8-octahydropyrano[3,2-f]indole, 4h

Prepared from bromoenynamide 3a (50 mg, 0.12 mmol), stannane 19e[27] (71 mg, 0.19 mmol) and PdCl₂(PPh₃)₂ (8.0 mg, 0.012 mmol, 10 mol%) using General Procedure F with heating for 15 h. Purification via column chromatography (petroleum ether → petroleum ether / EtOAc, 20:1) afforded 4h as a pale yellow oil (32 mg, 0.077 mmol, 64%); Rf 0.22 (petroleum ether / EtOAc, 10:1); IR (thin film, νₒ max/cm⁻¹) 2954, 2926, 2857, 2255, 1677, 1627, 1598, 1454, 1351, 1162, 1109, 1089, 910; ¹H NMR (500 MHz, CDCl₃) δH 7.70 (2H, d, J = 8.5 Hz, TsH), 7.26 (2H, d, J = 8.0 Hz, TsH), 3.96 (2H, dt, J = 7.0, 3.5 Hz, H8), 3.68 (1H, ddd, J = 12.5, 8.5, 6.0 Hz, H2), 3.55 (1H, ddd, J = 12.5, 9.0, 6.5 Hz, H2), 2.81 (1H, ddd, J = 13.5, 9.0, 7.0 Hz, H1'), 2.42 (3H, s, TsCH₃), 2.38-2.31 (1H, m, H1'), 2.24-2.12 (1H, m, H5), 2.10-2.01 (1H, m, H4/6), 1.94-1.84 (3H, m, H4, H6 and H7), 1.85-1.76 (2H, m, H4/6 and H7), 1.48-1.40 (2H, m, H3 and H2'), 1.37-1.22 (7H, m, H2' and H3'-5'), 1.05 (1H, ddd, J = 13.0, 8.5, 7.0, 6.0 Hz, H3), 0.87 (3H, t, J = 7.0 Hz, H6'); ¹³C NMR (125 MHz, CDCl₃) δC 147.8, 143.8, 136.0, 135.5, 129.7, 127.9, 126.4, 103.3, 66.0, 51.3, 38.0, 34.5, 31.9, 29.2, 28.6, 27.8, 27.2, 25.2, 23.0, 22.9, 21.7, 14.3; HRMS (ES⁺) calc. for C₂₉H₄₄N₂O₃S⁺ [M+H]⁺ 416.2254, found 416.2242.
5-Methyl-1-tosyl-7-(trimethylsilyl)-2,3,4,5-tetrahydro-1H-indole, 4i

Synthesised from ynamide 3d (110 mg, 0.275 mmol) stannane 19a (146 mg, 0.440 mmol) and PdCl2(PPh3)2 (19.3 mg, 0.0275 mmol, 10 mol%) using General Procedure F, to afford 4i as a colorless crystalline solid (69 mg, 0.191 mmol, 69%); mp 111 °C; Rf 0.53 (petroleum ether / EtOAc, 10:1); IR (thin film, ν_max / cm⁻¹) 2954, 1350, 1246, 1163, 1090, 901, 841; ¹H NMR (400 MHz, CDCl₃) δ_H 7.63 (2H, d, J = 8.2 Hz, TsH), 7.25 (2H, d, J = 8.2 Hz, TsH), 5.92 (1H, d, J = 2.3 Hz, H₆), 3.81 (1H, ddd, J = 12.5, 8.0, 3.0 Hz, H₂), 3.62 (1H, dt, J = 13.0, 9.5 Hz, H₂), 2.43 (3H, s, TsMe), 2.40-2.29 (1H, m, H₅), 1.89 (1H, dd, J = 17.5, 8.0 Hz, H₄), 1.79-1.65 (2H, m, H₃ and H₄), 1.56 (1H, dt, J = 17.0, 6.0 Hz, H₃), 1.08 (3H, d, J = 7.0 Hz, H₁'), 0.26 (9H, s, TMS); ¹³C NMR (101 MHz, CDCl₃) δ_C 143.6, 143.5, 139.9, 134.6, 133.0, 129.5, 129.0, 128.3, 50.4, 31.3, 30.3, 30.2, 21.6, 19.8, 0.9; HRMS (ES⁺) calc. for C₁₉H₂₈NO₂SSi [M+H]⁺ 362.1605, found 362.1597.

4-Methyl-N-(3-methylene-5-(trimethylsilyl)pent-4-yn-1-yl)benzenesulfonamide, 21a

Isolated as a side-product from cascade cyclization reactions of 3d, as a yellow oil (3 mg, 9.3 µmol, 18%); Rf 0.23 (petroleum ether / EtOAc, 10:1); IR (thin film, ν_max / cm⁻¹) 2959, 1599, 1437, 1332, 1250, 1161, 1094, 909; ¹H NMR (500 MHz, CDCl₃) δ_H 7.75 (2H, d, J = 8.0 Hz, TsH), 7.31 (2H, d, J = 8.0 Hz, TsH), 5.43 (1H, d, J = 1.0 Hz, =CH₂), 5.23 (1H, d, J = 1.5 Hz, =CH₂), 4.52 (1H, t, J = 6.0 Hz, NH), 3.17 (2H, app q, J = 6.5 Hz, H₁), 2.43 (3H, s, TsCH₃), 2.28 (2H, t, J = 6.5 Hz, H₂), 0.14 (9H, s, Si(CH₃)₃); ¹³C NMR (125 MHz, CDCl₃) δ_C 143.6, 137.2, 129.9, 127.7, 127.3, 125.2, 104.0, 96.0, 41.6, 37.0, 21.7, 0.0; HRMS (ES⁺) calc. for C₁₆H₂₃NNaO₂SSi [M+Na]⁺ 344.1111, found 344.1110.

4-Methyl-N-(3-methylene-5-(triisopropylsilyl)pent-4-ynyl)benzenesulfonamide, 21b

Isolated product from attempted Suzuki cascade cyclisation reactions with TIPS-substituted ynamide 3e; Rf 0.14 (petroleum ether / ether, 3:1); ¹H NMR (500 MHz, CDCl₃) δ_H 7.74 (2H, d, J = 8.1 Hz, TsH), 7.30 (2H, d, J = 8.1 Hz, TsH), 5.44 (1H, d, J = 1.5 Hz, =CH₂), 5.24 (1H, d, J = 1.5 Hz, =CH₂), 4.47 (1H, t, J = 6.2 Hz, NH), 3.20 (2H, app q, J = 6.4 Hz, H₁), 2.43 (3H, s, TsCH₃), 2.30 (2H, t, J = 6.4 Hz, H₂), 1.03 (21H, app s, Si(Pr)₃); ¹³C NMR (125 MHz, CDCl₃) δ_C 143.4, 137.0, 129.7, 127.6, 127.1, 124.8, 105.7, 92.1, 41.3, 37.2, 21.5, 18.5, 11.1; HRMS (ES⁺) calc. for C₂₂H₃₆NO₂SSi [M+H]⁺ 406.2231, found 406.2230.
7. Ynamide carbopalladation / Molander-Suzuki coupling / electrocyclization cascades

These were performed using general procedure J.

7-Hexyl-5-phenyl-1-tosyl-2,3,4,5-tetrahydro-1H-indole, 4d

Following General Procedure J, using ynamide 3a (20.0 mg, 0.0485 mmol), potassium (E)-styrenyl trifluoroborate (11.2 mg, 0.0534 mmol), Pd(PPh₃)₄ (2.8 mg, 2.4 µmol, 5 mol%), LiOH (4.7 mg, 0.194 mmol) in MeCN / H₂O (10:1, 0.25 mL), with heating to 85 °C for 2 h. Purification by column chromatography (Et₂O / petroleum ether, 9:1) gave amidodiene 4d as a pale yellow oil (10.6 mg, 50%). The data for this compound are as previously reported.[16]

7-Hexyl-1-tosyl-2,3,4,5-tetrahydro-1H-indole, 4e

Following General Procedure J, using ynamide 3a (20.0 mg, 0.0485 mmol), potassium vinyltrifluoroborate (7.2 mg, 0.0534 mmol), Pd(PPh₃)₄ (2.8 mg, 2.4 µmol, 5 mol%), LiOH (4.7 mg, 0.194 mmol) in MeCN / H₂O (10:1, 0.25 mL), with heating to 85 °C for 2 h. Purification by column chromatography (Et₂O / petroleum ether, 9:1) gave amidodiene 4e as a pale yellow oil (14.5 mg, 83%). Rf 0.44 (petroleum ether / EtOAc, 3:1); ¹H NMR (400 MHz, CDCl₃) δH 7.67 (2H, d, J = 8.0 Hz, TsH), 7.26 (2H, d, J = 8.0 Hz, TsH), 5.61 (1H, t, J = 4.5 Hz, H6), 3.76 (2H, t, J = 7.5 Hz, H2), 2.56-2.49 (2H, m, H5), 2.44 (3H, s, TsMe), 2.16-2.06 (2H, m, H6), 1.99-1.91 (2H, m, H4), 1.63 (2H, t, J = 7.5 Hz, H3), 1.50-1.39 (2H, m, H1’), 1.45-1.25 (2H, m, H2’); 1.36-1.25 (6H, m, H3’-5’), 0.88 (3H, t, J = 7.0 Hz, H6’). The data for this compound are as previously reported.[16]

7-Hexyl-5-propyl-1-tosyl-2,3,4,5-tetrahydro-1H-indole, 4j

Following General Procedure J, using ynamide 3a (20.0 mg, 0.0485 mmol), potassium (E)-trifluoro(pent-1-en-1-yl)-borate (9.4 mg, 0.0534 mmol), Pd(PPh₃)₄ (2.8 mg, 2.4 µmol, 5 mol%), LiOH (4.7 mg, 0.194 mmol) in MeCN / H₂O (10:1, 0.25 mL), with heating to 85 °C for 2 h. Purification by flash chromatography (Et₂O /
petroleum ether, 9:1) gave the amidodiene 4j as a pale yellow oil (17.2 mg, 88%); Rf 0.19 (petroleum ether / EtOAc (9:1)); \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ 7.68 (2H, d, J = 7.5 Hz, TsH), 7.26 (2H, d, J = 7.5 Hz, TsH), 5.43 (1H, br s, H6), 3.87 (1H, ddd, J = 13.0, 8.0 and 3.5, H2), 3.68 (1H, dt, J = 13.0, 9.3 Hz, H2'), 2.69-2.58 (1H, m, H10), 2.44 (3H, s, TSCH\textsubscript{3}), 2.41-2.22 (2H, m, H10' and H5), 1.94 (1H, dd, J = 17.5 and 8.0, H4), 1.83-1.65 (2H, m, H4' and H3), 1.63-1.52 (1H, m, H3'), 1.50-1.25 (12H, m, H7, H8, H11-H14), 0.94 (3H, t, J = 7.0 Hz, H15) and 0.91-0.85 (3H, m, H9). The data for this compound are as previously reported.\textsuperscript{[16]}

5-Cyclohexyl-7-hexyl-1-tosyl-2,3,4,5-tetrahydro-1H-indole, 4k

![Diagram of 5-Cyclohexyl-7-hexyl-1-tosyl-2,3,4,5-tetrahydro-1H-indole, 4k]

Following General Procedure J, using ynamide 3a (20.0 mg, 0.0485 mmol), potassium (E)-(2-cyclohexylvinyl)trifluoroborate (11.5 mg, 0.0534 mmol), Pd(PPh\textsubscript{3})\textsubscript{4} (2.8 mg, 2.4 µmol, 5 mol%), LiOH (4.7 mg, 0.194 mmol) in MeCN / H\textsubscript{2}O (10:1, 0.25 mL), with heating to 85 °C for 2 h. Purification by flash chromatography gave the amidodiene 4k as a pale yellow oil (17.6 mg, 82%). Rf 0.51 (petroleum ether / Et\textsubscript{2}O (7:3)); \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) 7.70-7.66 (2H, m, TsH), 7.30-7.22 (2H, m, TsH), 5.47 (1H, br s, H6), 3.89 (1H, ddd, J = 13.0, 7.5, 3.5 Hz, H2), 3.66 (1H, dt, J = 13.0, 9.5 Hz, H2'), 2.70-2.60 (1H, m, H14), 2.45 (3H, s, TsMe), 2.40-2.27 (1H, m, H14'), 2.22-2.04 (1H, m, H5), 1.92 (1H, t, J = 17.0 Hz, H4), 1.83 (1H, dd, J = 17.0, 8.5 Hz, H4'), 1.80-1.62 (4H, m, H3 and H15), 1.52-1.12 (11H, m, alkyl CH\textsubscript{2} and H10), 1.06-0.86 (2H, m, H13), 0.89-0.85 (3H, m, H19); The data for this compound are as previously reported.\textsuperscript{[16]}

5-Cyclopropyl-7-hexyl-1-tosyl-2,3,4,5-tetrahydro-1H-indole, 4p

![Diagram of 5-Cyclopropyl-7-hexyl-1-tosyl-2,3,4,5-tetrahydro-1H-indole, 4p]

Following General Procedure J, using ynamide 3a (20.0 mg, 0.0485 mmol), potassium (E)-(2-cyclopropylvinyl)trifluoroborate (9.3 mg, 0.0534 mmol), Pd(PPh\textsubscript{3})\textsubscript{4} (2.8 mg, 2.4 µmol, 5 mol%), LiOH (4.7 mg, 0.194 mmol), MeCN:H\textsubscript{2}O (10:1) (0.25 mL), heating to 85 °C for 2 h, gave after purification by column chromatography (Et\textsubscript{2}O:petroleum ether (9:1)), the amidodiene 4p as a pale yellow oil (14.5 mg, 75%). Rf 0.55 (petroleum ether / Et\textsubscript{2}O (7:3)); \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ 7.69-7.64 (2H, m, TsH), 7.25-7.22 (2H, m, TsH), 5.56 (1H, br d, J = 1.5 Hz, H6), 3.86 (1H, ddd, J = 13.0, 8.0 and 3.0, H2), 3.68 (1H, dt, J = 13.0, 9.5 Hz, H2'), 2.69-2.58 (1H, m, H12), 2.44 (3H, s, TsMe), 2.41-2.33 (1H, m, H12'), 2.09-1.92 (2H, m, H4), 1.78-1.68 (1H, m, H3), 1.63-1.39 (4H, m, H3', H5, H13), 1.37-1.25 (6H, m, H14-H16), 0.93-0.86 (3H, m, H17), 0.81-0.72 (1H, m, H10\textsubscript{a}), 0.55-0.40 (2H, m, H10\textsubscript{b}), 0.23-0.16 (1H, m, H10\textsubscript{a'}), 0.11-0.03 (1H, m, H10\textsubscript{b'}); The data for this compound are as previously reported.\textsuperscript{[16]}
5,7-Diphenyl-1-tosyl-2,3,4,5-tetrahydro-1H-indole, 4ae:

Following General Procedure J, using ynamide 3b (20.0 mg, 0.0495 mmol), potassium (E)-styrenyl trifluoroborate (11.4 mg, 0.0544 mmol), Pd(PPh₃)₄ (2.9 mg, 2.5 µmol, 5 mol%), LiOH (4.7 mg, 0.198 mmol), in MeCN / H₂O (10:1, 0.25 mL), with heating to 85 °C for 2 h. Purification by flash chromatography gave the amidodiene 4ae as a pale yellow oil (8.5 mg, 40%). Rₚ 0.40 (petroleum ether / EtOAc (10:1)); IR (thin film, v_max / cm⁻¹) 3059, 3028, 2926, 2845, 2253, 1598, 1493, 1447, 1353, 1164, 1090; ¹H NMR (400 MHz, CDCl₃) δ_H 7.62 (2H, d, J = 8.0 Hz, TsH), 7.48 (2H, dd, J = 8.0, 1.0 Hz, PhH), 7.37-7.34 (6H, m, PhH), 7.31-7.26 (2H, m, PhH), 7.23 (2H, d, J = 8.0 Hz, TsH), 6.06 (1H, d, J = 3.5 Hz, H6), 4.04-3.99 (1H, m, H2), 3.86-3.80 (1H, dt, J = 13.0, 9.0 Hz, H2'), 3.80-3.76 (1H, m, H5), 2.52-2.31 (2H, m, H4), 2.45 (3H, m, TsMe), 1.97 (2H, app t, J = 9.0 Hz, H3). The data for this compound are as previously reported.[¹⁶]

NB. Compound undergoes partial aerobic oxidation to the indoline.[¹⁶]

9-Hexyl-1,4-ditosyl-2,3,4,5,6,7-hexahydro-1H-benzo[e][1,4]diazepine, 4af

Following General Procedure J, using ynamide 3l (30.0 mg, 0.0504 mmol), potassium vinyltrifluoroborate (7.4 mg, 0.0554 mmol), Pd(PPh₃)₄ (2.9 mg, 2.5 µmol, 5 mol%), LiOH (4.8 mg, 0.201 mmol), MeCN:H₂O (10:1) (0.25 mL), heating to 85 °C for 3 h, gave after purification by column chromatography, the amidodiene 4af as a tacky colorless oil (18.4 mg, 80%). Rₚ 0.40 (petroleum ether / EtOAc (4:1)); IR (thin film, v_max / cm⁻¹) 2927, 2857, 1597, 1493, 1451, 1346, 1250, 1211, 1161, 1091, 1044, 962, 877, 815, 670; ¹H NMR (500 MHz, C₆D₆) δ_H 7.66-7.62 (2H, m, TsH), 7.50-7.45 (2H, dm, TsH), 7.37-7.34 (6H, m, PhH), 6.75 (2H, d, J = 8.0 Hz, TsH), 6.64 (2H, d, J = 8.0 Hz, TsH), 5.60 (1H, br app d, J = 6.5 Hz, H8), 4.09 (1H, dt, J = 15.0, 3.0 Hz, H5), 3.68 (1H, dd, J = 15.0, 1.0 Hz, H3), 3.44 (1H, br d, J = 13.0 Hz, H2), 3.07-3.01 (1H, m, H3'), 2.87-2.77 (2H, m, H2', H5'), 2.51-2.39 (1H, td, J = 18.5, 7.5 Hz, H6), 2.38-2.21 (2H, m, CH₂(CH₂)₃CH₂), 2.10-1.98 (1H, m, H7), 1.91 (3H, s, TsMe), 1.82 (3H, s, TsMe), 1.85-1.72 (2H, m, H6', H7'), 1.38-1.22 (8H, m, (CH₂)₃), 0.91 (3H, t, J = 7.5 Hz, CH₂CH₂); ¹³C NMR (125 MHz, CDCl₃) δ_C 143.5, 143.2, 139.4, 138.9, 137.7, 137.0, 136.7, 129.9, 129.9, 128.7, 128.1, 127.8, 122.5, 51.5, 49.6, 49.0, 32.6, 32.5, 30.6, 30.0, 29.5, 23.4, 22.8, 21.5, 21.5, 14.7; HRMS (ES+) calc. for C₂₆H₃₉O₃N₂S₂ [M+H]⁺ 543.2346, found 543.2347.

NB. Compound readily undergoes oxidation and decomposition.
8. Formal 4-endo-trig Heck cyclization of 3l to 8a

9-Hexyl-2-tosyl-2-azabicyclo[5.2.0]nona-1(9),6-diene, 8a

To a solution of ynamide 3k (30.0 mg, 0.0681 mmol) in PhMe (0.43 mL) was added Et₃N (57 µL, 0.409 mmol) and Pd(PPh₃)₄ (3.9 mg, 3.4 µmol, 5 mol%) and the mixture was heated to 85 °C for 16 h. The mixture was then cooled to rt and concentrated, and then purified by flash chromatography (petroleum ether / Et₂O, 9:1) to afford 8a as a colorless oil (17.6 mg, 72%). Rf 0.56 (petroleum ether / Et₂O (7:3)); IR (thin film, νmax/cm⁻¹) 3029, 2925, 2855, 1624, 1598, 1400, 1370, 1089, 681; ¹H NMR (500 MHz, CDCl₃) δH 7.71-7.67 (2H, m, TsH), 7.27 (2H, d, J = 8.0 Hz, PhH), 5.51 (1H, t, J = 7.5 Hz, H6), 3.61-3.58 (2H, m, H3), 2.63 (2H, br d, J = 1.5 Hz, H8), 2.43 (3H, s, TsCH3), 2.11-2.07 (2H, m, H10), 2.04 (2H, q, J = 7.5 Hz, H5), 1.44-1.36 (6H, m, H4, H11, H12), 1.35-1.28 (4H, m, H13, H14), 0.90 (3H, t, J = 7.0 Hz, H15); ¹³C NMR (125 MHz, CDCl₃) δC 143.4, 138.5, 137.5, 134.7, 134.6, 129.6, 127.3, 114.7, 52.3, 33.2, 31.7, 29.9, 28.6, 28.4, 26.0, 22.7, 21.7, 14.3; HRMS (ES+) calc. for C₂₁H₃₀NO₂S [M+H]⁺ 360.1992, found 360.1897.

9. Synthesis and Reductive Cyclizations of Bromoenynhydrazides 34a-c

Di-tert-butyl 1-(oct-1-yne-1-yl)hydrazine-1,2-dicarboxylate, 31

The procedure of Beveridge et al. was used for this reaction.²⁸[n-BuLi (1.44 mL, 3.60 mmol, 1.2 equiv., 2.5 M in THF) was added dropwise to a stirred solution of oct-1-yne (0.44 mL, 3.00 mmol, 1.0 equiv.) in THF
(15 mL) at −78 °C over 1-2 min. The mixture was stirred for 15 min at −78 °C, then a solution of di-tert-butyldicarboxylate (1.03 g, 4.50 mmol, 1.5 equiv.) in THF (9 mL) was added dropwise over 1-2 min, after which the cooling bath was removed and the reaction warmed to rt and stirred for a further 30 min. The reaction was quenched by the addition of NH₄Cl (15 mL, sat. aq.) and then diluted with EtOAc and water. The organic layer was separated, dried (MgSO₄) filtered through a short silica plug topped with Celite (EtOAc eluent), and concentrated. Purification via flash chromatography (petroleum ether / EtOAc, 20:1→10:1) afforded ynhydrazide 31 as a colorless oil (678 mg, 1.98 mmol, 66%); Rf 0.34 (petroleum ether / EtOAc, 10:1); ¹H NMR (500 MHz, CDCl₃) δH 2.29 (2H, t, J = 7.0 Hz, H5), 1.49 (9H, s, CO₂Bu), 1.48 (9H, s, CO₂Bu), 1.43-1.32 (4H, m, H6 and H7), 1.32-1.22 (4H, m, H8 and H9), 0.88 (3H, t, J = 7.0 Hz, H10); ¹³C NMR (125 MHz, CDCl₃) δC 154.2, 153.4, 152.9, 152.6, 127.4, 154.0, 153.6, 152.9, 152.6, 127.4, 127.0, 120.2, 119.2, 83.8, 82.4, 72.3, 56.8, 56.5, 31.5, 28.9, 28.6, 28.2, 28.0, 22.7, 18.5, 14.2; HRMS (ES⁺)

**Di-tert-butyl 1-(2-bromoallyl)-2-(oct-1-yn-1-yl)hydrazine-1,2-dicarboxylate, 32a**

![Diagram](image)

**Method A:** The procedure of Tšupova et al. was used for this preparation. To a vial containing K₂CO₃ (40 mg, 0.293 mmol, 2.0 equiv.), ground NaOH (20 mg, 0.511 mmol, 3.5 equiv.), n-Bu₄NHSO₄ (5 mg, 0.0146 mmol, 0.1 equiv.) and n-Bu₄NI (5 mg, 0.0146 mmol, 0.1 equiv.) was added a solution of ynhydrazide 31 (50 mg, 0.146 mmol, 1.0 equiv.) and 2,3-dibromopropene (29 µL, 0.293 mmol, 2.0 equiv.) in toluene (0.15 mL, 1 mL mmol⁻¹). The resulting mixture was stirred for 2 h at rt before being quenched with NH₄Cl (sat. aq.), diluted with EtOAc and water, and the layers separated. The organic layer was dried (MgSO₄) and concentrated. Purification via flash chromatography (petroleum ether / EtOAc, 20:1) afforded 32a as a colorless oil (50 mg, 0.108 mmol, 74%).

**Method B:** To a vial containing n-Bu₄NHSO₄ (5 mg, 0.0146 mmol, 0.1 equiv.) and n-Bu₄NI (5 mg, 0.0146 mmol, 0.1 equiv.) was added a solution of ynhydrazide 31 (50 mg, 0.146 mmol, 1.0 equiv.) and 2,3-dibromopropene (29 µL, 0.293 mmol, 2.0 equiv.) in toluene (1.5 mL, 10 mL mmol⁻¹). To this was added aq. NaOH (1.5 mL, 10 mL mmol⁻¹, 25% w/v) and the biphasic mixture was stirred rapidly for 1 h at rt before being quenched with NH₄Cl (sat. aq.), diluted with EtOAc and water, and the layers separated. The organic layer was dried (MgSO₄) and concentrated. Purification via flash chromatography (petroleum ether / EtOAc, 20:1) afforded 32a as a colorless oil (48.3 mg, 0.105 mmol, 72%); Rf 0.65 (petroleum ether / EtOAc, 10:1); IR (thin film) vₘₐₓ / cm⁻¹ 2959, 2933, 1730, 1301, 1256, 1150; ¹H NMR Broad signals due to rotameric forms of carbonates (500 MHz, CDCl₃) δH 5.98 (1H, br s, H5) and 5.91 (1H, br s, H5), 5.61 (1H, s, H5), 4.65-4.34 (1H, m, H3), 4.26-4.00 (1H, m, H3), 2.31 (2H, br s, H8), 1.63-1.44 (20H, m, H9 and 2 x CO₂Bu), 1.44-1.33 (2H, m, H10), 1.34-1.22 (4H, m, H11 and H12), 0.89 (3H, t, J = 7.0 Hz, H13); ¹³C NMR Broad signals due to rotameric forms of carbonates (125 MHz, CDCl₃) δC 154.0, 153.6, 152.9, 152.6, 127.4, 127.0, 120.2, 119.2, 83.8, 82.4, 72.3, 56.8, 56.5, 31.5, 28.9, 28.6, 28.2, 28.0, 22.7, 18.5, 14.2; HRMS (ES⁺)
calc. for C$_{2}$_{3}H$_{35}$Br$_{2}$NaO$_{4}$[M+Na]$^+$ 481.1672, found 481.1661.

3-Bromobut-3-en-1-yl 4-methylbenzenesulfonate, 33 (prepared as S2, above)

![Chemical structure](image)

To an ice-cooled solution of alcohol 10a (5.11 g, 33.8 mmol, 1.0 equiv.) in CH$_2$Cl$_2$ (2.6 mL) was added pyridine (5.5 mL, 67.7 mmol, 2.0 equiv.) and p-toluenesulfonyl chloride (9.68 g, 50.8 mmol, 1.5 equiv.). After addition, the reaction was warmed to rt and stirred for 3 h before being diluted with CH$_2$Cl$_2$. The organic layer was separated and washed with HCl (1M, aq.). The aqueous layer was extracted with CH$_2$Cl$_2$, and the combined organics washed with NaHCO$_3$ (sat., aq.), dried (MgSO$_4$) and concentrated. Purification via flash chromatography (petroleum ether / Et$_2$O, 8:1) afforded tosylate S2 as a colorless oil (10.3 g, 33.8 mmol, quant.); $R_f$ 0.21 (petroleum ether / Et$_2$O, 8:1); $^{1}$H NMR (400 MHz, CDCl$_3$) δH 7.79 (1H, d, $J$ = 8.0 Hz, ArH), 7.35 (2H, d, $J$ = 8.0 Hz, ArH), 5.65 (1H, app s, H4), 5.48 (1H, d, $J$ = 2.0 Hz, H4), 4.19 (2H, t, $J$ = 6.2 Hz, H1), 2.74 (2H, t, $J$ = 6.2 Hz, H2), 2.45 (3H, s, TsCH$_3$); $^{13}$C NMR (101 MHz, CDCl$_3$) δC 145.0, 132.8, 129.9, 128.0, 127.6, 120.2, 67.2, 40.7, 21.7. Data in accordance with literature values.$^{[11]}$

Di-tert-butyl 1-(3-bromobut-3-en-1-yl)-2-(oct-1-yn-1-yl)hydrazine-1,2-dicarboxylate, 32b

![Chemical structure](image)

The procedure of Tšupova et al. was used for this preparation.$^{[20]}$ To a vial containing K$_2$CO$_3$ (40 mg, 0.293 mmol, 2.0 equiv.), ground NaOH (20 mg, 0.511 mmol, 3.5 equiv.), Bu$_4$NHSO$_4$ (5 mg, 0.0146 mmol, 0.1 equiv.) and n-Bu$_4$NI (5 mg, 0.0146 mmol, 0.1 equiv.) was added a solution of ynhydrazide 31 (50 mg, 0.146 mmol, 1.0 equiv.) and tosylate 33 (89 mg, 0.293 mmol, 2.0 equiv.) in toluene (0.15 mL, 1 mL mmol$^{-1}$). The resulting mixture was stirred for 22 h at rt before being quenched with NH$_4$Cl (sat. aq.), diluted with EtOAc and water, and the layers separated. The organic layer was dried (MgSO$_4$) and concentrated. Purification via flash chromatography (petroleum ether / EtOAc, 20:1) afforded 32b as a colorless oil (38 mg, 0.080 mmol, 55%); $R_f$ 0.54 (petroleum ether / EtOAc, 10:1); IR (thin film) $\nu_{max}$/ cm$^{-1}$ 2979, 2932, 1719, 1368, 1300, 1254, 1147; $^{1}$H NMR Broad signals due to rotameric forms of both carbonates (500 MHz, CDCl$_3$) δH 5.68 (1H, s, H6), 5.46 (1H, s, H6), 3.81 (1H, br s, H3), 3.61 (1H, br s, H3), 2.76 (2H, br d, $J$ = 6.0 Hz, H4), 2.30 (2H, br s, H9), 1.58-1.33 (22H, m, H10, H11 and 2 x CO$_2$Bu), 1.28 (4H, br s, H12 and H13), 0.88 (3H, t, $J$ = 6.5 Hz, H14); $^{13}$C NMR Broad and multiple signals due to rotameric forms of both carbonates (125 MHz, CDCl$_3$) δC 154.0, 153.7, 153.1, 152.8, 130.7, 130.4, 118.9, 118.4, 83.7, 81.9, 73.1, 72.8, 71.6, 48.7, 47.2, 40.2, 39.4, 31.5, 28.9, 28.6, 28.5, 28.3, 28.1, 22.7, 18.6, 14.2; HRMS (ES$^+$) calc. for C$_{22}$H$_{37}$BrN$_2$NaO$_4$ [M+Na]$^+$ 495.1829; found 495.1820.

38
The preparation of iodide 34 was achieved according to the following Scheme:[30]

\[
\text{t-BuO} \quad \xrightarrow{\text{LDA; 2,3-dibromopropene}} \quad \text{t-BuO} \quad \xrightarrow{\text{LiAlH}_4} \quad \text{O} \quad \xrightarrow{\text{PPh}_3/\text{I}_2} \quad \text{I}
\]

\textit{t-Butyl-4-bromopent-4-enoate, S13}

The procedure of Baldwin et al. was used.[30] To a freshly prepared 1 M solution of LDA at −78 °C (17.2 mL, 17.2 mmol, 1.5 equiv., prepared from addition of \(n\)-BuLi (8.0 mL, 2.5 M) to a solution of \(i\)-Pr₂NH (2.8 mL) in THF (9.2 mL) at 0 °C), was added a solution of \textit{t}-butyl acetate (2.30 mL, 17.2 mmol, 1.5 equiv.) in THF (36 mL) dropwise. The reaction was stirred for 30 min at −78 °C, then 2,3-dibromopropene (1.2 mL, 11.5 mmol, 1.0 equiv.) was added dropwise. After stirring for 2 h −78 °C, the reaction was quenched with \(\text{NH}_4\text{Cl}\) (sat. aq.) and allowed to warm to rt, before being extracted with \(\text{Et}_2\text{O}\). The organic layers were combined, dried (MgSO₄) and concentrated. Purification via flash chromatography (petroleum ether / EtOAc, 10:1) afforded S13 as a colorless oil (2.15 g, 9.20 mmol, 80%); \(R_f\) 0.54 (petroleum ether / EtOAc, 10:1); \(^1\text{H NMR}\) (500 MHz, CDCl₃) \(\delta_H\) 5.63 (1H, d, \(J = 1.5\) Hz, H5), 5.43 (1H, d, \(J = 1.5\) Hz, H5), 2.72 (2H, t, \(J = 7.5\) Hz, H2), 2.49 (2H, td, \(J = 7.5\) Hz, H3), 1.45 (9H, s, C(CH₃)₃); \(^{13}\text{C NMR}\) (101 MHz, CDCl₃) \(\delta_C\) 171.2, 132.5, 117.3, 80.7, 36.8, 34.1, 28.1. Data in accordance with literature values.[30]

\textit{4-Bromopent-4-en-1-ol, S14}

The procedure of Baldwin et al. was used.[30] To a solution of LiAlH₄ (382 mg, 10.07 mmol, 1.1 equiv.) in \(\text{Et}_2\text{O}\) (18 mL) at 0 °C was added a solution of \textit{t}-butyl 4-bromopent-4-enoate S13 (2.15 g, 9.15 mmol, 1.0 equiv.) in \(\text{Et}_2\text{O}\) (18 mL). The reaction mixture was then stirred for 2 h at rt before being quenched with NaOH (sat. aq.). The aqueous layer was extracted with \(\text{Et}_2\text{O}\) and the combined organic layers were dried (MgSO₄) and concentrated \textit{in vacuo} to afford S14 as a pale yellow oil (0.85 g, 5.12 mmol, 56%); \(R_f\) 0.58 (petroleum ether / EtOAc, 1:1); \(^1\text{H NMR}\) (500 MHz, CDCl₃) \(\delta_H\) 5.62 (1H, d, \(J = 1.5\) Hz, H5), 5.43 (1H, d, \(J = 1.5\) Hz, H5), 3.69 (2H, t, \(J = 6.0\) Hz, H1), 2.55 (2H, t, \(J = 7.5\) Hz, H3), 1.84 (2H, quin, \(J = 7.5\) Hz, H2), 1.39 (1H, br s, OH); \(^{13}\text{C NMR}\) (125 MHz, CDCl₃) \(\delta_C\) 133.9, 117.0, 61.4, 37.7, 30.8. Data in accordance with literature values.[30]
2-Bromo-5-iodopent-1-ene, 34

The procedure of Baldwin et al. was used for this reaction.[30] To a solution of alcohol S14 (1.00 g, 6.06 mmol, 1.0 equiv.) in Et₂O:MeCN (38 mL, 3:1) was added PPh₃ (1.75 g, 6.66 mmol, 1.1 equiv.) and imidazole (453 mg, 6.66 mmol, 1.1 equiv.). The resultant solution was cooled to 0 °C, then iodine (1.69 g, 6.66 mmol, 1.1 equiv.) was added portionwise. After complete addition the reaction was warmed to rt and stirred for 1 h, before being filtered under reduced pressure, the solid being thoroughly washed with cold Et₂O, then the solvent was removed in vacuo. The crude mixture was redissolved in Et₂O and washed successively with 10% aq. Na₂S₂O₃ and brine before being dried (MgSO₄) and concentrated. Petroleum ether was then added to the crude residue and the reaction was filtered through a silica plug; concentration of the filtrate afforded iodide 34 as a colorless oil (1.29 g, 4.72 mmol, 78%); Rₚ 0.70 (petroleum ether / EtOAc, 10:1); ¹H NMR (400 MHz, CDCl₃) δH 5.68 (1H, d, J = 1.0 Hz, H1), 5.47 (1H, d, J = 1.5 Hz, H1), 3.19 (2H, t, J = 6.5 Hz, H5), 2.56 (2H, t, J = 7.0 Hz, H3), 2.06 (2H, quin, J = 7.0 Hz, H4); ¹³C NMR (101 MHz, CDCl₃) δC 132.2, 118.4, 41.7, 31.0, 5.2. Data in accordance with literature values.[30]

Di-tert-butyl 1-(4-bromopent-4-en-1-yl)-2-(oct-1-yn-1-yl)hydrazine-1,2-dicarboxylate, 32c

To a vial containing n-Bu₄NHSO₄ (5.0 mg, 0.0146 mmol, 0.1 equiv.) was added a solution of ynhydrazide 31 (50 mg, 0.146 mmol, 1.0 equiv.) and iodide 34 (80 mg, 0.293 mmol, 2.0 equiv.) in toluene (1.5 mL, 10 mL mmol⁻¹). To this was added NaOH (aq., 1.5 mL, 10 mL mmol⁻¹, 25% w/v) and the biphasic mixture was stirred vigorously at rt for 21 h, before being quenched with NH₄Cl (sat. aq.), diluted with EtOAc and water, and the layers separated. The organic layer was dried (MgSO₄) and concentrated. Purification via flash chromatography (petroleum ether / EtOAc, 10:1) afforded bromoenynhydrazide 32c as a colorless oil (41.2 mg, 0.84 mmol, 58%); Rₚ 0.49 (petroleum ether / EtOAc, 10:1); IR (thin film) νmax / cm⁻¹ 2980, 2933, 1740, 1716, 1393, 1148; ¹H NMR Broad signals due to rotameric forms of both carbonates (500 MHz, CDCl₃) δH 5.60 (1H, d, J = 1.5 Hz, H7), 5.42 (1H, br s, H7), 3.67-3.49 (1H, m, H3), 3.49-3.34 (1H, m, H3), 2.51 (2H, t, J = 6.5 Hz, H5), 2.28 (2H, t, J = 10.5 Hz, H10), 1.86 (2H, dt, J = 13.5, 7.0 Hz, H4), 1.57-1.33 (22H, m, H11, H12 and 2 x CO₂t-Bu), 1.33-1.07 (4H, m, H13 and H14), 0.87 (3H, t, J = 6.5 Hz, H15); ¹³C NMR Broad and multiple signals due to rotameric forms of both carbonates (125 MHz, CDCl₃) δC 154.4, 154.1, 153.3, 152.8, 133.9, 133.6, 117.1, 83.6, 83.4, 81.7, 81.6, 73.1, 72.7, 71.6, 46.9, 38.8, 31.5, 29.0, 28.6, 28.5, 28.3, 28.1, 25.9, 22.7, 18.6, 14.2; HRMS (ES⁺) calc. for C₂₃HₙBr₂NaO₄[M+Na⁺]⁺ 509.1985, found 509.1978.
(Z)-Di-tert-butyl 3-heptylidene-4-methylenepyrazolidine-1,2-dicarboxylate, 35a

Prepared by General Procedure H using bromoenynamide 32a (90 mg, 0.195 mmol) with heating for 1 h or by General Procedure I Method B using bromoenynamide 32a (90 mg, 0.195 mmol) with heating for 22 h. Purification via column chromatography (petroleum ether / EtOAc, 20:1) afforded the exocyclic diene 35a as a pale yellow oil (36.5 mg, 0.096 mmol, 49% from Procedure H, and 39.5 mg, 0.103 mmol, 53% from Procedure IB); Rf 0.44 (petroleum ether / EtOAc, 10:1); IR (thin film) νmax / cm⁻¹ 2978, 2929, 1712, 1456, 1392, 1368, 1326, 1151; ¹H NMR (500 MHz, CDCl₃) δH 5.64-5.57 (1H, m, H6), 5.30 (1H, t, J = 2.5 Hz, H13), 4.90 (1H, s, H13), 4.51 (1H, d, J = 15.0 Hz, H5), 3.87 (1H, d, J = 15.0 Hz, H5), 2.26-2.18 (2H, m, H7), 1.56-1.33 (22H, m, H8, H9 and 2 × CO₂t-Bu), 1.35-1.09 (4H, m, H10 and H11), 0.86 (3H, t, J = 7.0 Hz, H12); ¹³C NMR (125 MHz, CDCl₃) δC 156.0, 154.3, 141.5, 134.5, 115.9, 102.5, 82.0, 81.3, 50.7, 31.8, 29.5, 29.2, 29.1, 28.3, 28.3, 22.7, 14.2; HRMS (ES⁺) calc. for C₂₁H₃₆N₂NaO₄ [M+Na]⁺ 403.2567; found 403.2567.

The stereochemistry of 35a was assigned through ¹H NMR nOe experiments. A strong enhancement was seen between H6 and cis-H13. The stereochemistry of the dienes 35b and 35c was assigned by analogy.

(Z)-Di-tert-butyl 3-heptylidene-4-methylenetetrahydropyridazine-1,2-dicarboxylate, 35b

Prepared by General Procedure I Method B using bromoenynamide 32b (10 mg, 0.021 mmol) with heating for 30 min. Purification via column chromatography (petroleum ether → petroleum ether / EtOAc, 9:1) afforded the exocyclic diene 35b as a colorless oil (4.3 mg, 0.011 mmol, 52%); Rf 0.43 (petroleum ether / EtOAc, 10:1); IR (thin film) νmax / cm⁻¹ 2929, 1710, 1456, 1393, 1368, 1255, 1151; ¹H NMR Broad signals due to rotenamer forms of carbonates (500 MHz, CDCl₃) δH 5.72 (1H, s, H7), 5.22 (1H, s, H14), 4.83 (1H, s, H14), 3.99-3.85 (1H, m, H6), 3.45-3.29 (1H, m, H6), 2.52-2.41 (1H, m, H5), 2.34-2.18 (2H, m, H5 and H8), 2.16-2.06 (1H, m, H8), 1.46 (18H, s, 2 × CO₂t-Bu), 1.36-1.22 (8H, m, H9-H12), 0.87 (3H, t, J = 7.0 Hz, H13); ¹³C NMR Broad signals due to rotenamer forms of carbonates (125 MHz, CDCl₃) δC 154.5, 154.0, 133.2, 128.8, 123.5, 110.1, 96.3, 81.5, 80.7, 44.5, 32.0, 30.8, 29.9, 29.4, 29.1, 28.5, 28.3, 28.1, 22.8, 14.2; HRMS (ES⁺) calc. for C₂₂H₃₈N₂NaO₄ [M+Na]⁺ 417.2724; found 417.2706.
(Z)-Di-\textit{tert}-butyl 3-heptylidene-4-methylene-1,2-diazepane-1,2-dicarboxylate, 35c

Prepared by General Procedure H using bromoenynamide 32c (40 mg, 0.082 mmol) with heating for 1.5 h. Purification via column chromatography (petroleum ether \rightarrow petroleum ether / EtOAc, 9:1) afforded the exocyclic diene 35c as a colorless oil (5.2 mg, 0.012 mmol, 15%); \textbf{R_f} 0.43 (petroleum ether / EtOAc, 10:1); \textbf{IR} (thin film) \textit{ν} \textsubscript{max} / cm\textsuperscript{-1} 2930, 1715, 1455, 1392, 1366, 1323, 1152; \textbf{\textsuperscript{1}H NMR} Broad / doubled signals due to rotameric forms of carbonates (500 MHz, CDCl\textsubscript{3}) \textit{δ} H 5.64 (1H, dd, \textit{J} = 8.5, 5.5 Hz, H8), 5.22 (1H, s, H15), 4.84 (1H, s, H15), 4.23 (1H, d, \textit{J} = 14.0 Hz, H7), 2.96-2.83 (1H, m, H7), 2.49-2.40 (1H, m, H5), 2.15-1.98 (3H, m, H5 and H9), 1.85-1.76 (1H, m, H6), 1.71-1.59 (1H, m, H6), 1.51-1.42 (20H, m, 2 \times \text{CO}_2\textit{t}-\text{Bu} and H10), 1.37-1.22 (6H, m, H11-H13), 0.92-0.84 (3H, m, H14); \textbf{\textsuperscript{13}C NMR} Broad signals due to rotameric forms of carbonates (125MHz, CDCl\textsubscript{3}) \textit{δ} C 155.3, 151.4, 147.4, 137.4, 123.0, 113.1, 81.3, 81.0, 47.9, 34.3, 32.0, 30.8, 29.4, 29.0, 28.9, 28.5, 28.4, 22.8, 14.2; \textbf{HRMS} (ES\textsuperscript{+}) calc. for C\textsubscript{23}H\textsubscript{40}N\textsubscript{2}NaO\textsubscript{4} [M+Na]\textsuperscript{+} 431.2880; found 431.2875.
10. (Hetero-) Diels-Alder Cycloadditions of Amidodienes 5a, 4c and 4d

Diisopropyl 7-hexyl-1-tosyl-2,3-dihydro-1H-pyrrolo[2,3-d]pyridazine-5,6(4H,7H)-dicarboxylate, 36a

Di-iso-propylazodicarboxylate (19.5 µL, 0.099 mmol, 1.1 equiv.) was added dropwise to a stirred solution of diene 5a (30 mg, 0.099 mmol, 1.0 equiv.) in CH₂Cl₂ (1.0 mL). The reaction mixture was stirred for 3 h at rt, then diluted with CH₂Cl₂ (10 mL) and washed with NaHCO₃ (10 mL, sat., aq.). The organic layer was dried (MgSO₄), filtered and concentrated. The resulting crude material was purified by flash chromatography (petroleum ether / EtOAc, 5:1) to give 36a as a colorless oil (36 mg, 0.067 mmol, 75%); R瘠 0.41 (petroleum ether / EtOAc, 3:1); IR (thin film) νmax / cm⁻¹ 2928, 1720, 1381, 1168, 1105; ¹H NMR (500 MHz, δH) 7.80 (2H, d, J = 7.7 Hz, TsH), 6.95 (2H, d, J = 7.7 Hz, m-TsH), 5.76-5.62 (1H, br m, H7), 5.07-4.94 (2H, m, 2 x CH(CH₃)₂), 4.28 (1H, d, J = 16.5 Hz, H4), 3.53 (1H, d, J = 16.5 Hz, H4), 3.51-3.40 (2H, m, H2), 2.21 (1H, m, H10), 2.00 (3H, s, ArCH₂), 1.84-1.71 (2H, m, H11) 1.70-1.59 (2H, m, H10, H3), 1.60-1.49 (1H, m, H3), 1.43-1.25 (6H, m, H12-14), 1.25-1.05 (12H, m, 2 x CH(CH₃)₂), 0.99-0.83 (3H, m, H15); ¹³C NMR (125 MHz, δC) 156.5, 155.5, 143.7, 139.1, 135.8, 130.0, 128.8, 118.6, 70.6, 70.0, 56.5, 49.9, 43.8, 32.8, 32.2, 30.5, 29.5, 29.4, 27.6, 23.3, 22.5, 22.4, 22.3, 22.2, 21.3, 14.4; HRMS m/z (ES⁺) calc. for C₂₇H₄₅N₃NaO₆S [M+Na]⁺ 558.2608; found 558.2602.

Di-tert-butyl 7-hexyl-1-tosyl-2,3-dihydro-1H-pyrrolo[2,3-d]pyridazine-5,6(4H,7H)-dicarboxylate, 36b

Di-tert-butylazodicarboxylate (23 mg, 0.099 mmol, 1.1 equiv.) was added dropwise to a solution of 5a (30 mg, 0.099 mmol, 1.0 equiv.) in CH₂Cl₂ (1.0 mL). The reaction mixture was stirred at rt for 15 h, then diluted with CH₂Cl₂ (10 mL) and washed with NaHCO₃ (10 mL, sat. aq.). The organic layer was dried (MgSO₄), filtered and concentrated. The resulting crude material was purified by column chromatography (10% → 20% EtOAc in petroleum ether) to give 36b as a colorless oil (48 mg, 0.085 mmol, 95%); the ¹H NMR spectrum of this compound is broadened due to the highly rotameric nature of the product. Due to the thermal instability of the compound, variable temperature analysis could not be attempted, and as such ¹³C NMR spectroscopic analysis is not reported as signal coalescence could not be obtained. R瘠 0.38 (petroleum ether /
EtOAc, 4:1); 1H NMR (500 MHz, CDCl3) δH 7.83-7.62 (2H, br m, TsH), 7.32-7.20 (2H, br m, TsH), 5.44-5.19 (1H, br m, H9), 4.25 (1H, d, J = 16.7 Hz, H4), 3.83-3.74 (1H, m, H2), 3.68-3.48 (2H, br m, H2, H4), 2.46-2.37 (3H, br m, ArCH3), 2.15-2.05 (2H, m, H3), 2.00-1.90 (1H, m, H10), 1.68-1.22 (9H, m, H10, H12-14), 0.93-0.83 (3H, br m, H15); IR (thin film) νmax / cm⁻¹ 2928, 1703, 1393, 1367, 1164; HRMS m/z (ES⁺) calc. for C20H14N2NaO3S [M+Na]⁺ 586.2921; found 586.2930.

10-Hexyl-7-phenyl-1-tosyl-2,3,7,10-tetrahydropyrrolo[2,3-d][1,2,4]triazolo[1,2-a]pyridazine-6,8(1H,4H)-dione, 36c.

To a solution of 5a (30 mg, 0.090 mmol, 1.0 equiv.) in CH2Cl2 (0.5 mL) was added a solution of 4-phenyl-3H-1,2,4-triazole-3,5(4H)-dione 6c (18 mg, 0.099 mmol, 1.1 equiv.) in CH2Cl2 (0.5 mL). The reaction mixture was stirred at rt for 10 min. The reaction mixture was added to CH2Cl2 (10 mL), washed with sat. aq. NaHCO3 (10 mL), dried (MgSO4), filtered and concentrated in vacuo. The resulting crude material was purified by column chromatography (petroleum ether / EtOAc, 3:2) to give 36c as a colorless oil (39 mg, 0.077 mmol, 85%); Rf 0.29 (3:2, petroleum ether:EtOAc); 1H NMR (500 MHz, CDCl3) δH 7.69 (2H, d, J = 8.2 Hz, TsH), 7.57-7.53 (2H, m, PhH), 7.49 (2H, app t, J = 7.5 Hz, PhH), 7.39 (1H, t, J = 7.5 Hz, PhH), 7.35 (2H, d, J = 8.2 Hz, TsH), 5.47 (1H, br s, H10), 4.25 (1H, dd, J = 16.1, 0.6 Hz, H4), 3.98-3.81 (3H, m, H4, 2x H2), 2.45 (3H, s, ArCH3), 2.29-2.20 (1H, m, H3), 2.20-2.09 (2H, m, H3, H13), 2.06-1.96 (1H, m, H13), 1.48-1.21 (8H, m, H14-17), 0.87 (3H, t, J = 6.7 Hz, H18); 13C NMR (125 MHz, CDCl3) δC 153.0, 150.6, 144.5, 136.0, 133.2, 131.2, 130.0, 129.2, 128.2, 127.6, 125.3, 118.6, 54.2, 50.2, 44.3, 32.1, 31.6, 29.2, 29.2, 24.9, 22.6, 21.6, 14.0; IR (thin film) νmax / cm⁻¹ 2927, 1777, 1715, 1354, 1164; HRMS m/z (ES⁺) calc. for C20H14N2NaO3S [M+Na]⁺ 531.2036; found 531.2049.

N,N',N'-Tetrabenzylmethanediamine

According to the modified procedure of Heaney et al.[31] Dibenzyamine (500 mg, 97%, 2.46 mmol, 2.0 equiv.) was added dropwise to a mixture of formaldehyde (94 µL, 37 wt% in H2O, 1.23 mmol, 1.0 equiv.) in H2O (1.5 mL) and Et2O (0.5 mL) at 0 °C. The reaction mixture was stirred at rt overnight and then saturated with solid KOH. The aqueous layer was extracted with Et2O (2 × 15 mL). The combined organic layers were dried (MgSO4), filtered and concentrated in vacuo. The resulting crude material was purified by column chromatography (5:1, petroleum ether:EtOAc) to give the title compound as a colorless solid (385 mg, 0.95 mmol, 77%); m.p. 94-98 °C; Rf = 0.50 (5:1, petroleum ether:EtOAc); δH (400 MHz, CDCl3) 7.17-7.34 (20H, m, ArH), 3.60 (8H, CH2Ph), 3.08 (2H, N-CH2-N); δC (100 MHz, CDCl3) 139.7, 129.0, 128.1,
5,5-Dibenzyl-7-hexyl-1-tosyl-2,3,4,5,6,7-hexahydro-1H-pyrrolo[3,2-c]pyridin-5-ium iodide, 39d.

A solution of \(N,N,N',N'\)-tetrabenzylmethanediamine (200 mg, 0.49 mmol) in Et₂O (0.5 mL) was added dropwise to a solution of iodotrimethylsilane (73 µL, 0.49 mmol) in Et₂O (0.5 mL) at 0 °C. The reaction was warmed to rt and stirred for 20 min, and the resultant precipitate was collected by filtration, washed with Et₂O, and dried in vacuo to give \(N\)-benzyl-\(N\)-methylene-1-phenylmethanaminium iodide 6d (135 mg, 0.40 mmol, 82%).

To a solution of 5a (30 mg, 0.090 mmol, 1.0 equiv.) in CH₂Cl₂ (1.0 mL) was added \(N\)-benzyl-\(N\)-methylene-1-phenylmethanaminium iodide 6d (33 mg, 0.099 mmol, 1.1 equiv.). The reaction mixture was stirred for 18 h at rt, and then concentrated. The resulting crude material was purified by flash chromatography (4.5% MeOH in CH₂Cl₂) to give 36d as a yellow semi-solid (46 mg, 0.069 mmol, 76%); \(R_f\) 0.53 (5.0% MeOH in DCM); IR (thin film) \(\nu_{\text{max}}/\text{cm}^{-1}\) 2927, 1352, 1162; \(^1H\) NMR (500 MHz, CDCl₃) \(\delta\)H 7.81 (2H, d, \(J = 8.2\) Hz, TsH), 7.60 (2H, d, \(J = 6.9\) Hz, PhH), 7.58-7.52 (1H, m, PhH), 7.51-7.40 (5H, m, ArH), 7.29-7.23 (4H, m, TsH, ArH), 5.48 (1H, d, \(J = 12.9\) Hz, C\(\text{H}\)'Ph), 5.32 (1H, d, \(J = 12.6\) Hz, CH\(\text{H}\)'Ph), 4.62-4.49 (3H, m, C\(\text{H}\)'Ph, CH\(\text{H}\)'Ph, H6), 4.25 (1H, ddd, \(J = 12.9, 8.8, 2.2\) Hz, H2), 3.90-3.71 (3H, m, H4, H2), 3.37 (1H, br s, H7), 2.76 (1H, dd, \(J = 12.2, 11.4\) Hz, H6), 2.38-2.14 (3H, m, H3, H10), 2.28 (3H, s, ArCH₃) 1.49-1.39 (1H, m, H10), 1.37-1.14 (8H, m, H11-14), 0.89 (3H, t, \(J = 6.9\) Hz, H15); \(^{13}C\) NMR (125 MHz, CDCl₃) \(\delta\)C 145.3, 137.6, 134.6, 133.8, 133.1, 131.1, 131.0, 130.6, 129.5, 129.4, 127.3, 126.4, 125.9, 118.4, 64.2, 60.3, 58.4, 52.2, 50.3, 31.8, 31.3, 30.6, 29.7, 29.0, 25.3, 22.5, 21.5, 14.0; HRMS m/z (ESI) calc. for C₃₄H₄₃N₂O₂S \([M]^+\) 543.3040; found 543.3033.

(7-Hexyl-1-tosyl-2,3-dihydropyrrolo[2,3-d][1,2]oxazin-6(1H,4H,7H)-yl)(phenyl)methanone, 36e

To a solution of 5a (30 mg, 0.090 mmol, 1.0 equiv.) in CH₂Cl₂ (1.0 mL) was added Bu₄NIO₄ (90 mg, 0.207 mmol, 2.3 equiv.). Benzohydroxamic acid (27 mg, 0.198 mmol, 2.2 equiv.) was then added portionwise over 1 h. After consumption of starting material as judged by tlc, the reaction mixture was then partitioned between CH₂Cl₂ (5 mL) and NaHCO₃ (10 mL, sat. aq.). The aqueous layer was extracted with
further CH₂Cl₂ (2 x 5 mL). The combined organic layers were dried (MgSO₄), filtered and concentrated. The resulting crude material was purified by flash chromatography (30% → 40% EtOAc / petroleum ether) to give 36e as a yellow oil (as a single regioisomer) (40 mg, 0.085 mmol, 95%); R_f 0.50 (petroleum ether / EtOAc, 3:2); IR (thin film) ν max / cm⁻¹ 2928, 1642, 1354, 1164; ¹H NMR (500 MHz, CDCl₃) δ_H 7.78 (2H, d, J = 6.9 Hz, PhH), 7.60 (2H, d, J = 8.2 Hz, TsH), 7.54-7.48 (1H, m, PhH), 7.28-7.52 (2H, m, PhH), 7.36 (2H, d, J = 8.2 Hz, TsH), 4.79 (1H, br d, J = 6.9 Hz, H7), 4.45 (1H, d, J = 17.2 Hz, H4), 4.16 (1H, d, J = 17.2 Hz, H4), 3.82-3.67 (2H, m, H2), 2.47 (3H, s, ArC₃H₃), 2.09 (1H, dd, J = 15.4, 9.5 Hz, H3), 2.04-1.97 (1H, m, H10), 1.85-1.74 (1H, m, H3), 1.58-1.50 (1H, m, H10), 1.27-1.05 (8H, m, C11-C14), 0.85 (3H, t, J = 7.3 Hz, H15); ¹³C NMR (100 MHz, CDCl₃) δ_C 170.2, 144.5, 136.9, 133.3, 132.5, 131.2, 129.9, 128.8, 128.0, 127.6, 123.9, 80.8 (C7), 50.0 (C4), 43.4, 31.7, 31.1, 29.4, 28.8, 24.9, 22.5, 21.7, 14.1; HRMS m/z (ES⁺) calc. for C₂₆H₃₂N₂O₄S [M+Na]⁺ 491.1975; found 491.1974.

Note: An HSQC spectrum was used to correlate these proton and carbon chemical shifts and thus assign regioselectivity.

**tert-Butyl 7-hexyl-1-tosyl-2,3,4,7-tetrahydropyrrolo[3,2-d][1,2]oxazine-5(1H)-carboxylate 36f, and tert-Butyl 7-hexyl-1-tosyl-2,3,4,7-tetrahydropyrrolo[2,3-d][1,2]oxazine-6(1H)-carboxylate, 37f**

To a solution of 5a (30 mg, 0.090 mmol, 1.0 equiv.) in CH₂Cl₂ (1.0 mL) was added Bu₄NIO₄ (90 mg, 0.207 mmol, 2.3 equiv.). N-Boc-hydroxylamine (26 mg, 0.198 mmol, 2.2 equiv.) was then added portionwise over 1 h. After completion of the reaction as judged by tlc, the reaction mixture was partitioned between CH₂Cl₂ (5 mL) and NaHCO₃ (10 mL, sat. aq.). The aqueous layer was extracted with further CH₂Cl₂ (2 x 5 mL). The combined organic layers were dried (MgSO₄), filtered and concentrated. The resulting crude material was purified by flash chromatography (15% → 25% EtOAc / petroleum ether) to give regioisomeric products 36f and 37f, in a 1:8:1 ratio, as a pale yellow oil (41 mg, 0.088 mmol, 98%); For the purposes of characterization, 3 mg of each regioisomer was separated by semi-preparative HPLC.

Product 36f: HPLC (10% i-PrOH in hexane, 6.0 mL/min, t_R = 3.27 min); R_f 0.73 (petroleum ether / EtOAc, 3:2); IR (thin film) ν max / cm⁻¹ 2928, 1642, 1354, 1164; ¹H NMR (500 MHz, CDCl₃) δ_H 7.78 (2H, d, J = 6.9 Hz, PhH), 7.60 (2H, d, J = 8.2 Hz, TsH), 7.54-7.48 (1H, m, PhH), 7.28-7.52 (2H, m, PhH), 7.36 (2H, d, J = 8.2 Hz, TsH), 4.79 (1H, br d, J = 6.9 Hz, H7), 4.45 (1H, d, J = 17.2 Hz, H4), 4.16 (1H, d, J = 17.2 Hz, H4), 3.82-3.67 (2H, m, H2), 2.47 (3H, s, ArC₃H₃), 2.09 (1H, dd, J = 15.4, 9.5 Hz, H3), 2.04-1.97 (1H, m, H10), 1.85-1.74 (1H, m, H3), 1.58-1.50 (1H, m, H10), 1.27-1.05 (8H, m, C11-C14), 0.85 (3H, t, J = 7.3 Hz, H15); ¹³C NMR (100 MHz, CDCl₃) δ_C 170.2, 144.5, 136.9, 133.3, 132.5, 131.2, 129.9, 128.8, 128.0, 127.6, 123.9, 80.8 (C7), 50.0 (C4), 43.4, 31.7, 31.1, 29.4, 28.8, 24.9, 22.5, 21.7, 14.1; HRMS m/z (ES⁺) calc. for C₂₆H₃₂N₂O₄S [M+Na]⁺ 491.1975; found 491.1974.
Assignment of regioselectivity was made on the basis of $^1$H and $^{13}$C NMR chemical shifts, which show increased deshielding at the position adjacent to the oxygen atom. An HSQC spectrum was also used to correlate proton and carbon chemical shifts and thus assign regioselectivity.

| Atom | $\delta$ /ppm (36f) | $\delta$ /ppm (37f) |
|------|---------------------|---------------------|
| H4   | 4.00 (CH$_2$N)      | 4.53, 4.12 (CH$_2$O) |
| H7   | 4.99 (CHO)          | 5.21 (CHN)          |
| C4   | 45.1 (CN)           | 67.6 (CO)           |
| C7   | 79.1 (CO)           | 55.4 (CN)           |

7-Hexyl-5-phenyl-1-tosyl-1,2,3,4,5,7-hexahydropyrrolo[3,2-d]1,2]oxazine, 36g, and 7-Hexyl-6-phenyl-1-tosyl-1,2,3,4,6,7-hexahydropyrrolo[2,3-d]1,2]oxazine, 37g

To a solution of 5a (30 mg, 0.090 mmol, 1.0 equiv.) in CH$_2$Cl$_2$ (1.0 mL) was added nitrosobenzene (11 mg, 0.099 mmol, 1.1 equiv.). The reaction mixture was stirred for 10 min at rt. The reaction mixture was added
to CH₂Cl₂ (10 mL), washed with sat. aq. NaHCO₃ (10 mL), dried (MgSO₄), filtered and concentrated \textit{in vacuo}. The resulting crude material was purified by column chromatography (5:1, petroleum ether:EtOAc) to give regioisomeric products \textit{36g} and \textit{37g} in a 3.7:1 ratio as a yellow oil (32 mg, 0.073 mmol, 81%); For the purposes of characterisation, 2 mg of each regioisomer was separated by semi-preparative HPLC.

Product \textit{36g}: \textbf{HPLC} (1.5% \textit{i}-PrOH in hexane, 6.5 mL/min, \textit{t}ᵣ = 5.68 min; \textbf{R}_f 0.31 (petroleum ether / EtOAc, 5:1); \textbf{IR} (thin film) ν\textsubscript{max} / cm\textsuperscript{-1} 2926, 1354, 1163; \textbf{¹H NMR} (700 MHz, CDCl₃) δ\textsubscript{H} 7.67 (2H, d, \textit{J} = 8.1 Hz, Ts\textsubscript{H}), 7.32 (2H, dd, \textit{J} = 8.3, 7.4 Hz Ph\textsubscript{H}), 7.29 (2H, d, \textit{J} = 8.1 Hz, Ts\textsubscript{H}), 7.09 (2H, d, \textit{J} = 8.3 Hz, Ph\textsubscript{H}), 7.00 (1H, t, \textit{J} = 7.4 Hz, Ph\textsubscript{H}), 5.05 (1H, br d, \textit{J} = 8.5 Hz, H7), 3.8-3.7 (3H, m, 2 x H2, H4), 2.43 (3H, ArC\textsubscript{H}₃), 2.20-2.09 (2H, m, H3, H10), 1.98-1.90 (1H, m, H3), 1.90-1.82 (1H, m, H10), 1.44-1.19 (8H, m, H11-14), 0.91-0.87 (3H, m, H15); \textbf{¹³C NMR} (125 MHz, CDCl₃) δ\textsubscript{C} 150.2, 144.1, 139.3, 133.2, 129.8, 129.1, 128.0, 122.2, 115.6, 78.5 (C7), 51.8 (C4), 50.3, 32.0, 31.6, 29.7, 29.5, 29.3, 22.8, 21.8, 14.3; \textbf{HRMS m/z} (ES\textsuperscript{+}) calc. for C\textsubscript{25}H\textsubscript{32}N\textsubscript{2}O\textsubscript{3}NaO\textsubscript{3}S [M+Na\textsuperscript{+}] 463.2026; found 463.2034.

Product \textit{37g}: \textbf{HPLC} (1.5% \textit{i}-PrOH in hexane, 6.5 mL/min, \textit{t}ᵣ = 5.30 min; \textbf{R}_f 0.27 (petroleum ether / EtOAc, 5:1); \textbf{IR} (thin film) ν\textsubscript{max} / cm\textsuperscript{-1} 2925, 1353, 1163; \textbf{¹H NMR} (700 MHz, CDCl₃) δ\textsubscript{H} 7.70 (2H, d, \textit{J} = 8.3 Hz, Ts\textsubscript{H}), 7.31 (2H, dd, \textit{J} = 8.4, 7.5 Hz, Ph\textsubscript{H}), 7.24 (2H, d, \textit{J} = 8.3 Hz, Ts\textsubscript{H}), 7.09 (2H, d, \textit{J} = 8.4 Hz, Ph\textsubscript{H}), 6.97 (1H, t, \textit{J} = 7.5 Hz, Ph\textsubscript{H}), 4.84 (1H, br s, H7), 4.43 (1H, d, \textit{J} = 15.2 Hz, H4), 4.16 (1H, d, \textit{J} = 15.2 Hz, H4), 3.84-3.71 (2H, m, H2), 2.41 (3H, ArCH\textsubscript{3}), 2.12-2.05 (1H, m, H3), 1.97-1.90 (1H, m, H3), 1.90-1.83 (2H, m, H10), 1.51-1.42 (2H, m, H11), 1.32-1.18 (6H, m, H12-14), 0.92-0.79 (3H, m, H15); \textbf{¹³C NMR} (125 MHz, CDCl₃) δ\textsubscript{C} 148.1, 138.0, 134.2, 129.8, 129.2, 127.8, 121.5, 115.9, 65.0 (C4), 58.4 (C7), 50.0, 31.9, 31.3, 28.7, 26.7, 26.0, 22.8, 21.8, 14.2; \textbf{HRMS m/z} (ES\textsuperscript{+}) calc. for C\textsubscript{25}H\textsubscript{32}N\textsubscript{2}O\textsubscript{3}S [M+Na\textsuperscript{+}] 463.2026; found: 463.2030.

The assignment of regioselectivity was made on the basis of \textbf{¹H} and \textbf{¹³C} NMR chemical shifts, as follows, which show increased deshielding at the position adjacent to the oxygen atom:

| Atom | δ /ppm (36g) | δ /ppm (37g) |
|------|-------------|-------------|
| H4   | 3.80, 3.65 (CH\textsubscript{2}N) | 4.43, 4.16 (CH\textsubscript{2}O) |
| H7   | 5.05 (CHO)  | 4.84 (CHN)  |
| C4   | 51.6 (CN)   | 65.0 (CO)   |
| C7   | 78.3 (CO)   | 58.4 (CN)   |
To a stirred solution of dienamide 4c (80 mg, 0.214 mmol, 1.0 equiv.) in toluene (3 mL) at rt was added DDQ (58 mg, 0.256 mmol, 1.2 equiv.). After 2 h, the reaction was quenched with NaHCO₃ (5 mL, sat., aq.) and extracted with Et₂O. The combined organic layers were dried (MgSO₄) and concentrated. Flash chromatography (petroleum ether / EtOAc, 10:1) afforded 38 as an orange solid (80 mg, 0.133 mmol, 62%); Rf 0.44 (petroleum ether / EtOAc, 3:1); IR (thin film) νmax / cm⁻¹: 2930, 1704, 1579, 1454, 1359, 1244, 1168; ¹H NMR (500 MHz, CDCl₃) δH 7.67 (2H, d, J = 8.3 Hz, ArH), 7.33 (2H, d, J = 8.0 Hz, ArH), 3.88 (1H, ddd, J = 13.4, 8.4, 2.1 Hz, H2), 3.20 (1H, d, J = 1.3 Hz, H6), 3.02 (1H, ddd, J = 13.4, 11.0, 6.5 Hz, H2), 2.65-2.60 (3H, m, H1⁺, H4 and H5), 2.46 (3H, s, TsMe), 2.07 (1H, ddd, J = 14.4, 6.5, 2.1 Hz, H3), 1.50 (1H, ddd, J = 12.3, 3.8 Hz, H1⁺), 1.52-1.25 (9H, m, H3, H2’-H5’), 1.00 (3H, d, J = 6.3 Hz, Me), 0.90 (t, J = 6.9 Hz, H6’), 0.53 (app q, J = 8.9 Hz, H4);¹³C NMR (125 MHz, CDCl₃) δC 178.9, 178.0, 147.2, 145.8, 145.2, 136.4, 135.5, 130.1, 127.4, 123.9, 115.2, 114.2, 58.2, 56.1, 55.5, 54.9, 51.1, 33.0, 31.5, 29.7, 29.5, 29.4, 27.5, 22.6, 21.7, 21.4, 14.1; HRMS (ES⁺) calc. for C₃₅H₃₅Cl₅N₂NaO₅S [M+MeOH+Na]+ 654.1574; found 654.1567. For X-ray crystallography data, see end of SI.

*Of note:* The anisotropic effects of the nitriles lead to remarkable deshielding at H4β and H5 (2.6 ppm); and shielding at H4α (0.5 ppm).

7-Hexyl-5,8-diphenyl-1-tosyl-1,2,3,4,5,6-hexahydro-3a,6-(epoxyimino)indole, 39

To a solution of 4d (76 mg, 0.174 mmol, 1.0 equiv.) in CH₂Cl₂ (2.0 mL) was added nitrosobenzene (21 mg, 0.192 mmol, 1.1 equiv.). The reaction mixture was stirred at rt for 18 h, then diluted with CH₂Cl₂ (10 mL) and washed with NaHCO₃ (10 mL, sat. aq.). The organic layer was dried (MgSO₄), filtered and concentrated. The resulting crude material was purified by column chromatography (petroleum ether / EtOAc, 5:1) to give 39 as a yellow oil (71 mg, 0.131 mmol, 75%); Rf 0.28 (petroleum ether / EtOAc, 5:1); IR (thin film) νmax / cm⁻¹: 2927, 1597, 1488, 1355, 1165; ¹H NMR (500 MHz, CDCl₃) δH 7.29-7.17 (7H, m, ArH), 6.97-6.93 (3H, m, ArH), 4.31 (1H, d, J = 2.8 Hz, H6), 4.08 (1H, ddd, J = 12.3, 7.9, 2.2 Hz, H2), 3.84 (1H, ddd, J = 12.3, 10.7, 6.7 Hz, H2), 3.78 (1H, ddd, J = 9.4, 5.3, 2.9 Hz, H5), 2.51 (1H, ddd, J = 13.0, 9.6 Hz, H4), 2.41 (3H, s, ArCH₃), 2.06 (1H, ddd, J = 14.0, 6.8, 2.2 Hz, H3), 1.74 (1H, m, ArH), 1.50 (2H, m, ArH).
1.93 (1H, ddd, J = 14.1, 11.9, 5.0 Hz, H12), 1.76 (1H, ddd, J = 14.0, 10.9, 7.9 Hz, H3), 1.34 (1H, dd, J = 13.0, 5.4 Hz, H4), 1.06 (2H, app quin, J = 7.3 Hz, H16), 0.96-0.82 (4H, m, H14, H15), 0.77 (3H, t, J = 7.4 Hz, H17), 0.60-0.42 (2H, m, H13); δC (125 MHz, CDCl3) 151.1, 144.1, 142.1, 136.3, 135.7, 129.8, 128.5, 128.4, 128.1, 127.5, 126.9, 125.6, 122.7, 117.8, 81.1 (C10), 69.5 (C6), 51.4 (C2), 42.8 (C5), 37.8 (C4), 32.4 (C12), 31.9 (C3), 31.4, 29.4, 25.7, 22.3, 21.6, 14.0; HRMS m/z (ES+1 calc. for C33H38N2NaO3S [M+Na] 565.2495; found 565.2490.

The regiochemical assignment of this cycloadduct is made, as previously, on the basis of 1H and 13C NMR chemical shift analysis:

| Atom  | δ /ppm (39) |
|-------|-------------|
| H6    | 4.31 (CHN)  |
| C6    | 69.5 (CN)   |
| C10   | 81.1 (CO)   |

7-Hexyl-5-phenyl-6-(phenylamino)-1-tosyl-2,3,3a,4,5,6-hexahydro-1H-indol-3a-ol, 41.

![Chemical structure](image)

To a solution of 39 (24 mg, 0.044 mmol, 1.0 equiv.) in MeCN / H2O (0.7 mL / 0.1 mL) was added Mo(CO)6 (17 mg, 0.066 mmol, 1.6 equiv.). The reaction mixture was stirred for 10 min at rt, then NaBH4 (5.0 mg, 0.13 mmol, 3.0 equiv.) added. The reaction mixture was heated to 90 °C for 20 h, then cooled to rt and filtered through Celite, eluting with CH2Cl2. The solution was dried (MgSO4), filtered and concentrated. The resulting crude material was purified by column chromatography (petroleum ether / EtOAc, 5:1) to give 41 as a yellow oil (14.0 mg, 0.026 mmol, 58%); Rf 0.27 (petroleum ether / EtOAc, 5:1); 1H NMR (500 MHz, CDCl3) δH 7.87 (2H, d, J = 8.2 Hz, TsH), 7.37 (2H, d, J = 8.2 Hz, TsH), 7.28-7.22 (2H, m, PhH), 7.22-7.17 (1H, m, PhH), 7.15 (2H, d, J = 7.3 Hz, PhH), 7.06 (2H, app t, J = 7.9 Hz, NPhH), 6.65 (1H, t, J = 7.3 Hz, NPhH), 6.48 (2H, d, J = 7.9 Hz, NPhH), 3.91 (1H, d, J = 9.7 Hz, H6), 3.80 (1H, td, J = 10.1, 7.9 Hz, H2), 3.64 (1H, br s, NH), 3.44 (1H, td, J = 9.9, 1.5 Hz, H2), 3.35 (1H, ddd, J = 13.1, 10.0, 2.9 Hz, H5), 2.72 (1H, ddd, J = 14.5, 9.2, 7.1 Hz, H10), 2.45 (3H, s, ArCH3), 2.23-2.17 (1H, m, H10), 2.18 (dd, J = 13.3, 2.7 Hz, H4) 2.12 (1H, ddd, J = 13.0, 7.8, 1.7 Hz, H3), 2.03 (1H, br s, OH), 1.87 (1H, app t, J = 13.4 Hz, H4), 1.72 (1H, dt, J = 13.0, 9.6 Hz, H3), 1.46-1.04 (8H, m, H11-14), 0.83 (3H, t, J = 6.9 Hz, H15); 13C NMR (125 MHz, CDCl3) δC 147.5, 144.3, 143.2, 136.5, 135.5, 135.0, 129.7, 129.0, 128.4, 128.2, 127.9, 126.7, 117.6, 114.4, 74.7 (C=OH), 60.9 (C6), 47.6 (C2), 42.1 (C5), 40.4 (C4), 38.0 (C3), 31.5, 29.6, 28.8, 27.4, 22.6, 21.6, 14.1; IR (thin film) νmax / cm⁻¹ 3504, 3396, 2926, 1601, 1497, 1325, 1159; HRMS m/z (ES+) calc. for
The assignment of regio- and stereochemistry of the cycloaddition is supported by this compound; ^1H–^1H NMR J values imply the following conformation due to large axial-axial coupling around H4–H6:

\[
\begin{align*}
N\text{-}(2\text{-(1S,3R)-5-Hexyl-4-oxo-3-((4-oxocyclohexa-2,5-dien-1-ylidene)amino)oxy)-1,2,3,4-tetrahydro-[1,1'-biphenyl]-3-yl)ethyl}-4\text{-methylbenzenesulfonamide, 43}
\end{align*}
\]

According to the procedure of Miller and co-workers:^{33} To a solution of 41 (35 mg, 0.064 mmol, 1.0 equiv.) in EtOAc / MeCN (1 mL, 1:1) was added a solution of NaIO₄ (62 mg, 0.290 mmol, 4.5 equiv.) in H₂O (0.5 mL), followed by RuCl₃ (0.5 mg, 0.0016 mmol, 0.025 equiv.). The reaction mixture was stirred at rt, open to air, for 2 h. The mixture was then partitioned between EtOAc (5 mL) and brine (5 mL). The aqueous layer was extracted with EtOAc (3 x 5 mL), then the combined organic extracts were dried (MgSO₄), filtered and concentrated. The resulting crude material was purified by flash chromatography (petroleum ether / EtOAc, 4:1) to give 43 as a yellow oil (7.0 mg, 0.012 mmol, 19%); R_f 0.25 (petroleum ether / EtOAc, 4:1); ^1H NMR (500 MHz, CDCl₃) δH 7.69 (2H, d, J = 8.2 Hz, TsH), 7.61 (1H, dd, J = 10.4, 2.5 Hz, H10), 7.40-7.34 (2H, m, PhH), 7.33-7.28 (1H, m, PhH), 7.26 (2H, d, J = 8.2 Hz, TsH), 7.17 (2H, d, J = 7.3 Hz, PhH), 7.10 (1H, dd, J = 10.1, 2.5 Hz, H10), 6.62 (1H, br s, H6), 6.54-6.47 (2H, m, H11), 4.72 (1H, t, J = 6.0 Hz, NH), 3.87-3.80 (1H, m, H1), 3.07-3.00 (2H, m, H20), 2.75 (1H, ddd, J = 14.7, 4.9, 1.6 Hz, H2), 2.43-2.35 (1H, m, H13), 2.40 (3H, s, ArCH₃), 2.20-2.11 (3H, m, H19, H13), 2.09-2.02 (1H, m, H2), 1.42-1.19 (8H, m, H14-17), 0.88-0.82 (3H, m, H18); ^13C NMR (125 MHz, CDCl₃) δC 194.8 (C4), 187.1 (C12), 150.0 (C9), 147.3 (C6), 143.6, 143.0, 138.4 (C5), 136.9, 136.8, 133.0, 130.7, 129.8, 129.2, 127.68, 127.51, 127.2, 124.1, 85.3 (C3), 41.6 (C2), 39.9 (C1), 38.3 (C20), 33.7 (C19), 31.8, 30.2, 29.1, 28.4, 22.8, 21.7, 14.2; IR (thin film) ν max / cm⁻¹ 3279, 2925, 1685, 1641, 1329, 1159, 1094, 988; HRMS m/z (ES⁺) calc. for C₃₃H₃₈N₂NaO₃S [M+Na]^+ 597.2394; found 597.2401.
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12. Copies of $^1$H and $^{13}$C NMR spectra for novel or key compounds.

$^1$H: 500 MHz, CDCl$_3$
$^{13}$C: 125 MHz, CDCl$_3$
1\(^1\text{H}\): 400 MHz, CDCl\(_3\)

1\(^{13}\text{C}\): 100 MHz, CDCl\(_3\)

10a

Br

OH

1

4

10a

H: 400 MHz, CDCl\(_3\)

C: 100 MHz, CDCl\(_3\)
$^{1}$H: 400 MHz, CDCl$_3$

Data according to literature values. $^{[1]}$
$^{13}$C-NMR Spectrum

$^1$H: 400 MHz, CDCl$_3$

$^{13}$C: 100 MHz, CDCl$_3$
Data in accordance with literature values.\textsuperscript{[2],[3]}
$^{1}H$: 400 MHz, CDCl$_3$

$^{13}C$: 100 MHz, CDCl$_3$
Data in accordance with literature values.\cite{2}
Data identical to literature values.\textsuperscript{[4]}
1H: 500 MHz, CDCl₃
1³C: 125 MHz, CDCl₃
$^{13}$C: 125 MHz, CDCl$_3$
9d

$^1$H: 400 MHz, CDCl₃
$^{13}$C: 100 MHz, CDCl₃
$^1$H: 400 MHz, CDCl$_3$
$^{13}$C: 100 MHz, CDCl$_3$
$\text{F}_3\text{C}\text{-}\text{NHBr}$

$^1\text{H}$: 400 MHz, CDCl$_3$

$^{13}\text{C}$: 100 MHz, CDCl$_3$
NTsBoc

S5

$^1$H: 400 MHz, CDCl$_3$

$^{13}$C: 100 MHz, CDCl$_3$
Data in accordance with literature values.\textsuperscript{[5]}
NHTs  Br

9i

$^{1}H$: 500 MHz, CDCl$_3$

$^{13}C$: 125 MHz, CDCl$_3$
BocTsN \( \text{Ts} \) \( \text{Br} \)

**S7**

\(^1\text{H}: 400 \text{ MHz, CDCl}_3\)

*unstable compound*
Bromoalkynes

13a

$^1$H NMR (400 MHz, CDCl$_3$)
$^{13}$C NMR (100 MHz, CDCl$_3$)
13b

$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (100 MHz, CDCl$_3$)
Br

13c

$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (100 MHz, CDCl$_3$)
13d

$^1$H NMR (400 MHz, CDCl$_3$)
$^{13}$C NMR (100 MHz, CDCl$_3$)
TIPS

13e

$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (100 MHz, CDCl$_3$)
SB
$^1$H: 400 MHz, CDCl$_3$
$^{13}$C: 101 MHz, CDCl$_3$
HO

\textbf{15}

$^1$H: 400 MHz, CDCl$_3$

$^{13}$C: 101 MHz, CDCl$_3$
SC

$^1$H: 400 MHz, CDCl$_3$
$^{13}$C: 101 MHz, CDCl$_3$
$^1$H: 400 MHz, CDCl$_3$

unstable compound
\[ ^1\text{H}: 400\text{ MHz, CDCl}_3 \]

\[ ^{13}\text{C}: 101\text{ MHz, CDCl}_3 \]
$^1$H: 400 MHz, CDCl$_3$
$^{13}$C: 101 MHz, CDCl$_3$

**13g**

![Chemical Structure](image)
13h

$^1$H: 400 MHz, CDCl$_3$

$^{13}$C: 101 MHz, CDCl$_3$

unstable compound
VT NMR – Stille cascade cyclization: isolation of intermediate triene 20 from NMR reaction of 3a and 4a

Blue spectrum indicates isolated mixture of triene intermediate (20), starting material 3a (red), product 4a (green), and amide (ynamide hydrolysis product) in a 1 : 0.23 : 0.8 : 0.5 ratio.

The assignment of these characteristic peaks is as follows: $^1$H NMR (300 MHz; CDCl$_3$): $\delta$ 6.50 (1H, unresolved dq, $J = 15.7$ Hz, H3), 6.03 (1H, dq, $J = 15.6$, 6.8 Hz, H4), 5.04 (d, $J = 0.3$ Hz, H2), 4.88 (s, H1).

Irradiation of H2 (orange) shows enhancement at H3 and H1; Irradiation of H3 (pink) shows enhancement at H2.
Stille Cascade

\[
\begin{align*}
1\text{H NMR (400 MHz, CDCl}_3) \\
13\text{C NMR (125 MHz, CDCl}_3)
\end{align*}
\]
$^1$H NMR (500 MHz, CDCl$_3$)

$^13$C NMR (125 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (100 MHz, CDCl$_3$)
$^{1}$H NMR (500 MHz, CDCl$_3$)
$^{13}$C NMR (125 MHz, CDCl$_3$)
$^1$H NMR (500 MHz, CDCl$_3$)  
$^{13}$C NMR (125 MHz, CDCl$_3$)
$^1$H NMR (500 MHz, CDCl$_3$),
$^{13}$C NMR (125 MHz, CDCl$_3$)
$^{1}$H NMR (500 MHz, CDCl$_3$)  
$^{13}$C NMR (125 MHz, CDCl$_3$)
21a

$^1$H NMR (500 MHz, CDCl$_3$)

$^{13}$C NMR (125 MHz, CDCl$_3$)
21b

$^1\text{H NMR}$ (500 MHz, CDCl$_3$)

$^{13}\text{C NMR}$ (125 MHz, CDCl$_3$)
**Suzuki-Molander Cascades**: Data for compounds 4d, 4e, 4j, 4k, 4p, 4ae has been reported previously.\[^{[6]}\]

\[\text{\textbullet\textsuperscript{1}H: 400 MHz, CDCl}_3\]

\[\text{ppm}\]

\[2.00\quad 5.03\quad 2.05\quad 0.98\quad 0.97\quad 0.96\quad 0.99\quad 0.97\quad 4.36\quad 2.20\quad 2.25\quad 2.25\quad 7.94\quad 2.09\]

\[\text{ppm}\]

\[2.45\quad 3.29\quad 1.60\quad 2.19\quad 2.09\quad 3.41\quad 2.21\quad 2.12\quad 2.18\quad 2.35\quad 2.33\quad 7.10\quad 3.55\]
$^1$H: 400 MHz, CDCl$_3$
\( ^1\text{H} \): 400 MHz, CDCl\(_3\)

\textbf{4p}

\textbf{4ae}

\( ^1\text{H} \): 400 MHz, CDCl\(_3\)
$^1$H: 500 MHz, C$_6$D$_6$

$^{13}$C: 125 MHz, C$_6$D$_6$
Formal 4-endo-trig cyclization product

\[ \text{Ts} \]

8a

$^1$H: 500 MHz, CDCl$_3$

$^{13}$C: 125 MHz, CDCl$_2$
Ynhydrazides

\( ^2 \text{NHBOc} \)
\( \text{BocN} \)

31
\( ^1 \text{H: 500 MHz, CDCl}_3 \)
\( ^13 \text{C: 125 MHz, CDCl}_3 \)
32a

$^1$H: 500 MHz, CDCl$_3$

$^{13}$C: 125 MHz, CDCl$_3$
$^{13}$C: 125 MHz, CDCl$_3$
32c
$^1$H: 500 MHz, CDCl$_3$
$^{13}$C: 125 MHz, CDCl$_3$
35a

$^1$H: 500 MHz, CDCl$_3$

$^{13}$C: 125 MHz, CDCl$_3$
H3–H2 nOe

35a

\[ \text{H}^1 \text{H}: 500 \text{ MHz, CDCl}_3 \]

\[ ^{13}\text{C}: 125 \text{ MHz, CDCl}_3 \]
$35b$

$^1$H: 500 MHz, CDCl$_3$

$^{13}$C: 125 MHz, CDCl$_3$
Note: rotameric forms of Boc groups lead to doubling and broadening of signals
(Hetero-) Diels-Alder Cycloadditions of Amidodienes 5a, 4c and 4d

$^{1}H$: 500 MHz, $d_{8}$-tol, 363 K

$^{13}C$: 125 MHz, $d_{8}$-tol, 363 K
A $^{13}$C NMR could not be obtained for this compound due to broad / unresolved peaks at RT, and decomposition of the compound at higher temperatures (loss of Boc groups).

Other spectroscopic and physical properties of this cycloadduct closely resemble 36a, supporting assignment (including HRMS).
$^{1}$H: 500 MHz, CDCl$_3$

$^{13}$C: 125 MHz, CDCl$_3$
$^1$H: 500 MHz, CDCl$_3$
$^{13}$C: 125 MHz, CDCl$_3$
$^1$H: 500 MHz, CDCl$_3$

$^{13}$C: 125 MHz, CDCl$_3$
HSQC, 500 MHz, CDCl₃

36e
36f (major)
$^1$H: 500 MHz, CDCl$_3$
$^{13}$C: 125 MHz, CDCl$_3$

37f (minor)
$^1$H: 500 MHz, CDCl$_3$
$^{13}$C: 125 MHz, CDCl$_3$
HPLC-purified 36f

36f (major)

$^1$H: 500 MHz, CDCl$_3$

$^{13}$C: 125 MHz, CDCl$_3$
HPLC-purified 37f

37f (minor)

$^1$H: 500 MHz, CDCl$_3$

$^{13}$C: 125 MHz, CDCl$_3$
These spectra are of a mixture of the cycloadducts, 3.7:1 ratio. For the purposes of additional characterization, small amounts of each could be separated by HPLC. The amount isolated was only sufficient to obtain a 700 MHz $^1$H NMR spectrum (see below).
HPLC-purified 36g/37g

H4/C4, 36g (major) (C–N)
H4/C4, 37g (minor) (C–O)
H7/C7, 36g (major) (C–O)
H7/C7, 37g (minor) (C–N)

36g (major)
HSQC, 500 MHz, CDCl3

37g (minor)
HSQC, 500 MHz, CDCl3
36g (major)
$^1$H: 700 MHz, CDCl$_3$

37g (minor)
$^1$H: 700 MHz, CDCl$_3$
\[ \text{NTs} \]

\[ \text{Me} \]

\[ \text{38} \]

$^1$H: 500 MHz, CDCl$_3$

$^{13}$C: 125 MHz, CDCl$_3$
$^{13}$C: 125 MHz, CDCl$_3$
$^1$H: 500 MHz, CDCl$_3$
$^{13}$C: 125 MHz, CDCl$_3$

**41**

![Chemical Structure](image)
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