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Cross-Enyne and Ring-Closing Metathesis Cascade: A Building-Block Approach Suitable for Diversity-Oriented Synthesis of Densely Functionalized Macroheterocycles with Amino Acid Scaffolds

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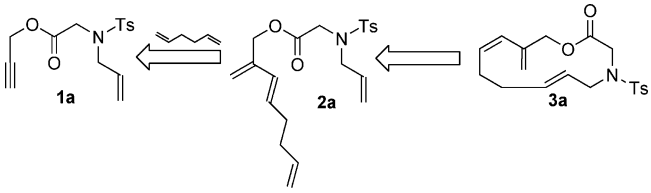
Suitably functionalized glycine derivatives undergo a cross-enyne and ring-closing metathesis cascade to generate macroheterocyclic ring systems in good yield. These macrocycles, prepared on the basis of a fragment coupling strategy, consist of 13–16-membered rings. To this end, 1,5-hexadiene was found to be a promising cross-coupling partner to generate macrocycles by this tandem metathesis sequence.

The ability to design complex molecules in a simple and straightforward manner seems to be a long-lasting dream of chemists. In this regard, nature uses various enzymes to assemble intricate macrocycles of diverse structural features.[1] For example, the biosyntheses of various tricyclic terpenes involve C_5-isoprene units as a starting point. Macroheterocycles are generally present as core units in natural products (e.g. epothilone and erythromycin) or cyclophane derivatives. Most of these systems, other than natural products and cyclophanes, were prepared to study aromaticity.[2] In general, saturated or unsaturated nonaromatic macroheterocycles are relatively rare in the literature. Recently, diversity-oriented synthesis (DOS)[3] has been actively pursued with the aim of discovering "drug-like" lead molecules. Although several diversity-oriented approaches have been reported for small molecules,[4] they are rare for macroheterocycles.[5] Therefore, a general and simple strategy for the diversity-oriented synthesis of macrocycles is highly desirable. Recent work from our group[6] and others[7] has shown that it is possible to design biologically relevant diverse skeletons of small molecules starting with simple starting materials such as β-naphthol by using the Claisen rearrangement and ring-closing metathesis (RCM) as the key steps. In this regard, synthetic methodologies that can deliver skeletal diversity are in great demand. In view of our continued interest in this area, we sought a simple and novel approach based on "fragment coupling strategy" to generate diverse macrocyclic frames starting with amino acid derivatives by using a cross-enyne metathesis–ring-closing metathesis cascade (Scheme 1).



Scheme 1.

Metathetic strategies such as RCM, ring-closing enyne metathesis (RCEM) and cross-enyne metathesis (CEM) protocols are powerful tools in organic synthesis for C–C bond formation sequence.[8] Various heterocyclic systems have been prepared by using different types of metathetic protocols.[9] To this end, amino acids found extensive use in the synthesis of heterocycles.[10] Recently, we reported the synthesis of various N-containing medium-sized heterocycles by using glycine equivalents.[11] Macrocyclic ring formation involves an intramolecular cyclization reaction of a bifunctional molecule such as **1a**; it is not a favourable process, and the activation entropy is quite negative. Several other side reactions that compete with cyclization are intermolecular oligomerization (dimerization) and polymerization. Under high-dilution conditions one can obtain cyclized products. A variety of reagents have been developed for macrocyclization reactions. In view of these facts, the synthesis of the macrocyclic system is not a trivial exercise. In the present study, we identified enyne substrate **1a** as a potential candidate to test our ideas for designing macrocycles by a metathesis cascade.[12] Compound **1a** can undergo RCEM as well as CEM to generate interesting and unknown macrocyclic frames. The amino acid building blocks, such as **1a**, are strategically designed to accommodate multifunctional groups of diverse structural elements. In our strategy (Scheme 1), diversity can be generated by

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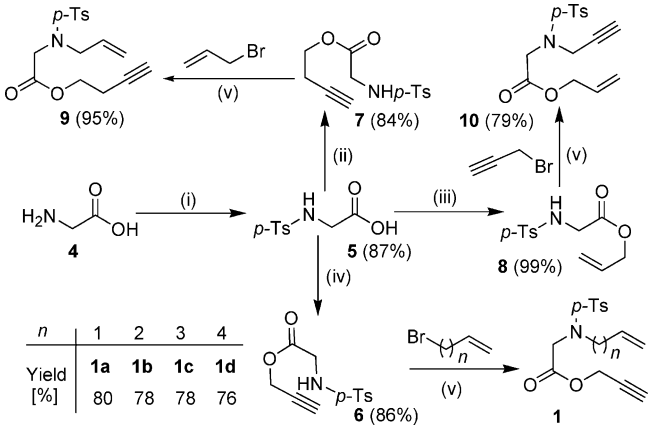
(1) varying the length of the chain attached to nitrogen, (2) varying the length of the chain attached to oxygen, (3) altering substituents at the α carbon atom, to be precise, by varying the amino acid (natural, nonnatural, α-amino acid, β-amino acid, etc.) and (4) changing the alkylation sequence at the nitrogen and/or oxygen atoms. Moreover, introduction of diversity is also feasible by using more than one of the methods stated above. These ideas clearly illustrate the potential of this strategy for the generation of various macroheterocyclic systems. The additional advantage of this methodology is that the double bond position in the newly formed ring can be altered by changing the alkylation sequence.

To start, tosylglycine **5** was prepared by using a literature procedure in 87% yield.[13] Later on, esterification of tosyl derivative **5** was carried out by using a Dean–Stark assembly with propargyl alcohol, 3-butyne-1-ol and allyl alcohol to yield compounds **6** (86%), **7** (84%) and **8**[14] (99%) (Scheme 2). These compounds were fully characterized by ^{1}H and ^{13}C NMR spectroscopy. Next, *N*-alkenylation was achieved by treatment of compound **6** with various bromo-alk-1-enes in the presence of K_2CO_3 in CH_3CN to deliver various enyne substrates. Along similar lines, compound **7** was treated with allyl bromide to yield **9** in 95% yield. When tosyl derivative **8** was treated with propargyl bromide, building block **10** was obtained in 79% yield. The presence of a singlet due to α-CH_2 at 4.01 ppm, the absence of an NH proton signal at 5.0 ppm and the presence of characteristic olefinic signals in the ^{1}H NMR spectrum supported these structures. All the products were characterized by ^{1}H and ^{13}C NMR spectroscopy as well as HRMS.



Scheme 2. Reagents and conditions: (i) 1. NaOH, H_2O, *p*-TsCl; 2. 1 N HCl; (ii) but-4-yn-1-ol, benzene, *p*-TsOH; (iii) allyl alcohol, benzene, *p*-TsOH; (iv) propargyl alcohol, benzene, *p*-TsOH; (v) CH_3CN, K_2CO_3, reflux.

Having enyne building blocks **1a**–**d**, **9** and **10** in hand, we proceeded to the cross-metathesis protocol of these substrate with 1,5-hexadiene in the presence of Grubbs' 2nd generation catalyst (Figure 1). Earlier, Diver and coworkers used 1,5-hexadiene to prepare various cyclohexadiene derivatives.[15]

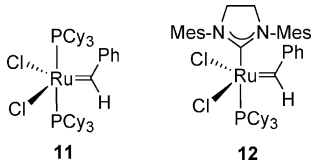
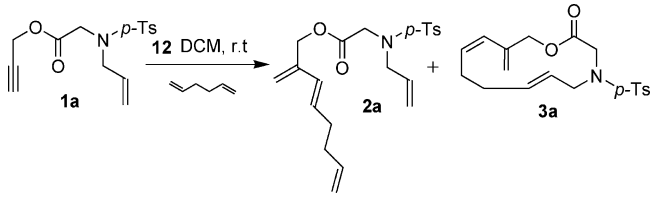


Figure 1. Grubbs' catalysts used in metathesis.

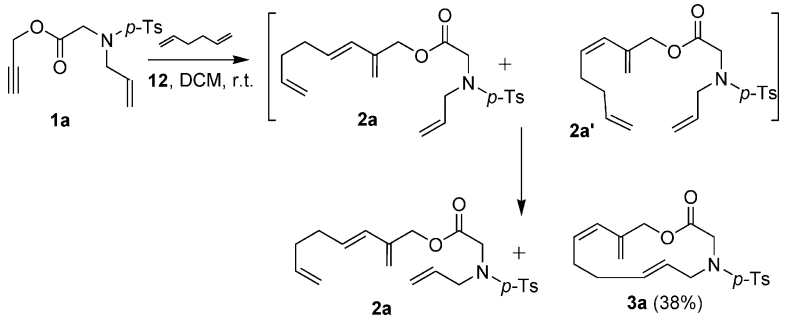
Apart from CEM, the possibility of a one-pot cross-enyne metathesis followed by RCM in these systems clearly opens up a new door for the synthesis of novel macrocycles. To test this hypothesis, enyne building block **1a** was treated with Grubbs' 2nd generation catalyst in the presence of 1,5-hexadiene as a connector. Gratifyingly, the reaction proceeded smoothly, and the two products were isolated by column chromatography. NMR spectral analysis of these compounds proved that **2a** is a CEM product, whereas **3a** is a CEM–RCM cascade product (Scheme 3). No intramolecular RCEM products were obtained during this procedure.



Scheme 3.

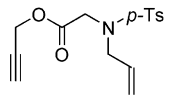
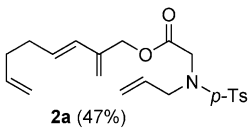
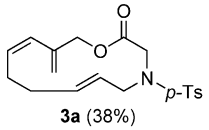
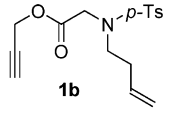
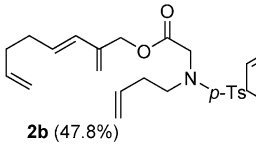
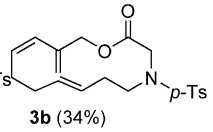
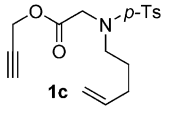
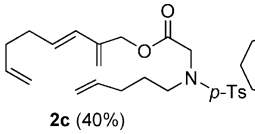
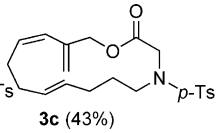
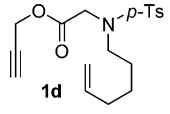
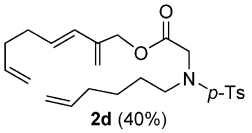
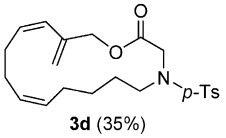
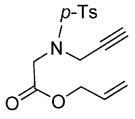
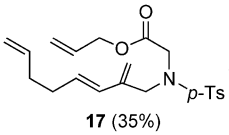
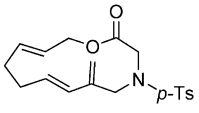
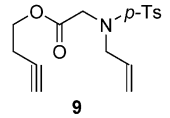
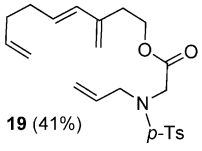
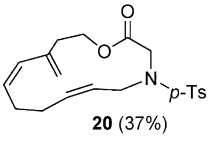
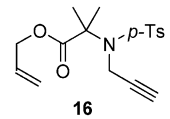
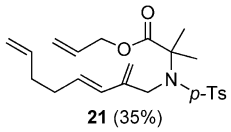
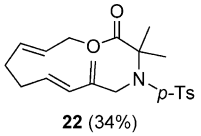
When **2a**, obtained from the metathesis, was subjected to RCM, the formation of **3a** was not observed. It seems there are two possible open-chain compounds with different conformations (**2a** and **2a′**) when 1,5-hexadiene undergoes intermolecular cross-metathesis with enyne building block **1a**. Among these isomers, **2a′** undergoes intramolecular ring closer to give **3a**, whereas **2a** remains intact (Scheme 4). The formation of an acyclic product (CEM product) suggests that first a CEM and then a RCM pathway is involved. Macrocycle formation is entropically driven due to the intramolecular nature of the ring closure with 1,5-hexadiene.

Along similar lines, enyne substrates **1b**–**d** and **9** were subjected to the CEM–RCM cascade. Several macrocycles of varying ring size, from 13–16-membered ring systems were obtained in good yield (Table 1). The structures of these products were deduced on the basis of their NMR spectroscopic and HRMS data. When compound **10** was subjected to similar reaction conditions, the desired products were isolated in good yield (Table 1, Entry 5). It is well known that *gem* dimethyl groups at the α carbon atom of glycine play a crucial role in conformational aspects of oligopeptides as a result of the Thorpe–Ingold effect.[16] Therefore, compound **15** was prepared from α-aminoisobutyric acid (AIB) by esterification with allyl alcohol followed by *N*-tosylation. Treatment of tosyl derivative **15** with propargyl bromide in DMF in the presence of K_2CO_3 gave enyne **16** in 92% yield (Scheme 5). The presence of two absorption bands at 3277 and 2371 cm^{-1} for the acetylene moiety indicated the formation of compound **16**. Also, the



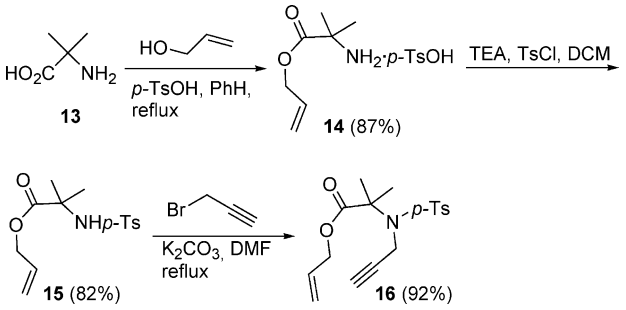
Scheme 4.

Table 1. List of various macroheterocyclic derivatives prepared by a CEM–RCM metathesis cascade.

Entry	Substrate	Products (% yield)	
1	 1a	 2a (47%)	 3a (38%)
2	 1b	 2b (47.8%)	 3b (34%)
3	 1c	 2c (40%)	 3c (43%)
4	 1d	 2d (40%)	 3d (35%)
5	 10	 17 (35%)	 18 (25%)
6	 9	 19 (41%)	 20 (37%)
7	 16	 21 (35%)	 22 (34%)

appearance of a triplet at δ = 2.22 (t, J = 2.31 Hz) ppm and the absence of an NH signal in the ^{1}H NMR spectrum further support the product formation.

When compound **16** was subjected to the metathesis protocol under similar reaction conditions, the desired products were isolated in good yield (Table 1, Entry 7). The IR spectra of these products showed a strong absorption peak at 1741 cm^{-1} due to the carbonyl moiety. Disappearance of the characteristic propargyl pattern in the ^{1}H NMR spectra and the appearance of new signals corresponding to the alkene moiety suggested the formation of the required product. The structures are further supported by their HRMS spectroscopic data. In all these cases, formation of the regular RCEM product was not observed. It is known that the substrates similar to that of **10** did not undergo RCEM.[17]



Scheme 5.

In conclusion, novel and unknown macroheterocyclic rings of varied size (13–16) were prepared by using a CEM–RCM cascade in good yield. These macrocycles are built from four building blocks; viz. glycine, propargyl alcohol, unsaturated alkene and 1,5-hexadiene. 1,5-Hexadiene is found to be a useful and promising connector for CEM, and we believe that the presence of 1,5-hexadiene in this strategy is crucial for the successful assembly of these macrocycles. Although we focused our strategy on glycine- and AIB-based amino acid scaffolds in the present study, this methodology can be extended to other natural and nonnatural amino acid scaffolds to prepare libraries of macroheterocyclic compounds.

Experimental Section

General Remarks: Melting points are uncorrected. Analytical thin-layer chromatography (TLC) was performed on (10 × 5 cm) glass plates coated with Acme's silica gel G or GF 254 (containing 13% calcium sulfate as a binder). Visualization of the spots on TLC plates was achieved either by exposure to iodine vapour or UV light. Flash chromatography was performed by using Acme's silica gel (100–200 mesh). Petroleum ether refers to fraction having boiling point 60–80 °C. Yields refer to the chromatographically isolated yield. Grubbs' catalysts (1st and 2nd generation) were purchased from Aldrich Chemical Co. (Milwaukee, WI, USA). All the commercial-grade reagents were used without further purification. Infrared spectra were recorded with a Nicolet 400 FTIR spectrometer in KBr/$CHCl_3$/CCl_4 and the absorptions are reported in cm^{-1}. ^1H NMR spectra were determined with a Varian 400 MHz spectrometer as $CDCl_3$ solutions. Coupling constants (*J* values) are given in Hertz (Hz). Chemical shifts are expressed in parts per million (ppm) downfield from internal reference tetramethylsilane. The high-resolution mass measurements were carried out by using a micromass Q-Tof spectrometer.

2-(4-Methylphenylsulfonamido)acetic Acid (5): To partially dissolved glycine (**4**; 7.5 g, 100 mmol) in distilled water (20 mL) was added a solution of NaOH (2 N, 50 mL) followed by the portionwise addition of *p*-toluenesulfonyl chloride (26.7 g, 140 mmol). The reaction mixture was vigorously stirred and a solution of NaOH (1 N) was added portionwise to maintain a pH ≈ 9 at 20 °C (ice–water cooling). After complete consumption of alkali, stirring was continued at room temperature for an additional 1 h. Unreacted acid chloride was removed by filtration, and the reaction mixture was acidified with HCl (5 N) at 0 °C to pH 2; some solid precipitated out. The aqueous solution with solid precipitate was stored in the refrigerator overnight; the crystals were collected by filtration, washed with cold water and dried in air and finally in vacuo. Yield: 20 g, 87%. M.p. 147 °C (ref.[13] 147 °C).

General Procedure for Esterification of 5: To a suspension of **5** in benzene was added *p*-toluenesulfonic acid (catalytic amount) and allyl alcohol (1.2 equiv.), and reaction mixture was heated at reflux with stirring. The water generated was removed by using a Dean–Stark trap. After complete consumption of **5** (TLC monitoring, 4 h), benzene was removed, and the obtained semisolid was taken up in EtOAc and washed with water; the aqueous layer was extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with brine, dried with Na_2SO_4 and concentrated in vacuo. The product thus obtained was recrystallized form petroleum ether/EtOAc, and the product was obtained as white shiny crystals.

Prop-2-ynyl 2-(4-methylphenylsulfonamido)acetate (6): To a suspension of **5** (1.0 g, 4.4 mmol) in benzene (30 mL) was added *p*-toluenesulfonic acid (10 mg) and propargyl alcohol (0.293 g, 0.3 mL, 5.23 mmol), and the reaction mixture was heated at reflux with stirring. The water formed during the reaction was removed by using a Dean–Stark trap. After complete conversion of **5** (TLC monitoring, 4 h), benzene was remove, and the obtained semisolid was taken up in EtOAc and washed with water; the aqueous layer was extracted with EtOAc (3 × 25 mL). The combined organic layer was washed with brine, dried with Na_2SO_4 and concentrated in vacuo. The product thus obtained was recrystallized form petroleum ether/EtOAc to give shiny white crystals. Yield: 1 g, 86%. M.p. 99 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.43 (s, 3 H), 2.49 (t, *J* = 2.6 Hz, 1 H), 3.84 (d, *J* = 5.5 Hz, 2 H), 4.61 (d, *J* = 1.6 Hz,2 H), 5.09 (t, *J* = 5.5 Hz, 1 H), 7.35 (d, *J* = 8.5 Hz, 2 H), 7.75 (d, *J* = 8.5 Hz, 2 H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 21.6, 44.1, 53.2, 75.9, 76.6, 127.3, 129.9, 136.1, 144.1, 168.3 ppm. HRMS (Q-TOF): calcd. for $C_{12}H_{14}NO_4S$ $[M + H]^+$ 268.0644; found 268.0643.

But-3-ynyl 2-(4-Methylphenylsulfonamido)acetate (7): To a suspension of **5** (1.0 g, 6.54 mmol) in benzene (30 mL) was added *p*-toluenesulfonic acid (10 mg) and but-3-yn-1-ol (0.55 g,7.85 mmol), and the reaction mixture was heated at reflux with stirring and water was removed by using a Dean–Stark trap. After complete conversion of **5** (TLC monitoring, 4.5 h), benzene was remove, and the obtained semisolid was taken up in EtOAc and washed with water; the aqueous layer was extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with brine, dried with Na_2SO_4 and concentrated in vacuo. The product thus obtained was recrystallized form petroleum ether/EtOAc and obtained as shiny white crystals. Yield: 1.55 g, 84%. M.p. 78 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.99 (t, *J* = 2.6 Hz, 1 H), 2.41–2.47 (m, 2 H), 2.44 (s, 3 H), 3.82 (br. s, 2 H), 4.11 (t, *J* = 6.8 Hz, 2 H), 5.01 (br. s, 1 H), 7.31 (d, *J* = 8.1 Hz, 2 H), 7.75 (d, *J* = 8.1 Hz, 2 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 18.8, 21.5, 44.1, 63.3, 70.3, 79.4, 127.3, 129.8, 143.8, 168.7 ppm. HRMS (Q-TOF): calcd. for $C_{13}H_{15}NNaO_4S$ $[M + Na]^+$ 304.0619; found 304.0626.

Allyl 2-(4-Methylphenylsulfonamido)acetate (8): To a suspension of **5** (3 g, 13 mmol) in benzene (100 mL) was added *p*-toluenesulfonic acid (10 mg) and allyl alcohol (0.912 g, 1.1 mL, 15.7 mmol), and reaction mixture was heated at reflux with stirring. The water was removed by using a Dean–Stark trap. After complete consumption of **5** (TLC monitoring, 4 h), benzene was removed, and the remaining semisolid was taken up in EtOAc and washed with water; the aqueous layer was extracted with EtOAc (3 × 25 mL). The combined organic layer was washed with brine, dried with Na_2SO_4 and concentrated in vacuo. The product thus obtained was recrystallized form petroleum ether/EtOAc and obtained as white shiny crystals. Yield: 3.5 g, 99%. M.p. 65–67 °C (ref.[13] 59–61 °C). ^1H NMR (400 MHz, $CDCl_3$): δ = 2.46 (s, 3 H), 3.83 (d, *J* = 5.7 Hz, 2

H), 4.55 (d, J = 5.9 Hz, 2 H), 5.12 (br. s, 1 H), 5.25–5.31 (m, 2 H), 5.78–5.89 (m, 1 H), 7.33 (d, J = 7.68 Hz, 2 H),7.78 (d, J = 7.5 Hz, 2 H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 21.6, 44.2, 66.4, 119.3, 127.3, 129.8, 131.1, 136.2, 143.9, 168.6 ppm. HRMS (Q-TOF): calcd. for $C_{12}H_{15}NNaO_4S$ $[M + Na]^+$ 292.0619; found 292.0628.

Prop-2-ynyl 2-(*N*-Allyl-4-methylphenylsulfonamido)acetate (1a): To a solution of **6** (500 mg, 1.83 mmol) in acetonitrile was added K_2CO_3 (776 mg, 5.61 mmol) under an atmosphere of nitrogen. Then, allyl bromide (272 mg, 0.2 mL, 2.24 mmol) was added slowly by syringe. The resulting light-brown solution was stirred at 90 °C for 8 h. Then, the reaction mixture was cooled (0 °C) and diluted with ethyl acetate. The reaction mixture was filtered over Celite with the help of a sintered funnel. The combined organic layer was concentrated in vacuo and then dissolved in ethyl acetate (30 mL). This solution was washed with water and brine, dried with $MgSO_4$ and concentrated in vacuo to yield an oily product. Purification of the crude product by column chromatography (SiO_2; petroleum ether/ethyl acetate, 11:1) gave compound **1a** (460 mg, 80%) as a thick liquid. Yield: 460 mg, 80%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.43 (s, 3 H), 2.41 (t, J = 2.4 Hz, 1 H), 3.84 (d, J = 6.6 Hz, 2 H), 4.07 (s, 2 H), 4.61 (d, J = 1.2 Hz, 2 H), 5.15–5.21 (m, 2 H), 5.62–5.75 (m, 1 H), 7.35 (d, J = 8.1 Hz, 2 H), 7.73 (d, J = 8.3 Hz, 2 H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 21.6, 46.8, 50.8, 52.6, 75.5, 76.9, 120.2, 127.4, 129.7, 132.1, 136.6, 143.7, 168.2 ppm. HRMS (Q-TOF): calcd. for $C_{15}H_{17}NNaO_4S$ $[M + Na]^+$ 330.0776; found 330.0771.

Prop-2-ynyl 2-[*N*-(But-3-enyl)-4-methylphenylsulfonamido]acetate (1b): To a solution of **6** (100 mg, 0.374 mmol) in acetonitrile was added K_2CO_3 (110 mg, 0.8 mmol) under an atmosphere of nitrogen. 4-Bromobut-1-ene (64.8 mg, 0.05 mL, 0.48 mmol) was added slowly by syringe. The resulting light-brown solution was stirred at 90 °C for 8 h (TLC monitoring) before the reaction was cooled. The reaction mixture was diluted with ethyl acetate and filtered over Celite with the help of a sintered funnel. The organic layer was concentrated in vacuo and then dissolved in ethyl acetate (20 mL), washed with water and brine, dried with Na_2SO_4 and concentrated in vacuo to yield an oily product. Purification of the crude product by column chromatography (SiO_2; petroleum ether/ethyl acetate, 11:1) gave compound **1b** (490 mg, 74%) as a thick liquid. Yield: 490 mg, 74%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.28–2.37 (m, 2 H), 2.43 (s, 3 H), 2.49 (t, J = 2.4 Hz, 1 H), 3.29–3.63 (m, 2 H), 4.12 (s, 2 H), 4.63 (d, J = 2.7 Hz, 2 H), 5.02–5.09 (m, 2 H), 5.65–5.73 (m, 1 H), 7.29 (d, J = 8.3 Hz, 2 H), 7.72 (d, J = 8.3 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.8, 32.7, 47.9, 48.2, 52.9, 75.7, 76.9, 117.6, 127.6, 129.8, 134.6, 136.8, 143.7, 168.4 ppm. HRMS (Q-TOF): calcd. for $C_{16}H_{20}NO_4S$ $[M + H]^+$ 322.1113; found 322.1121.

Prop-2-ynyl 2-[*N*-(Pent-4-enyl)-4-methylphenylsulfonamido]acetate (1c): To a solution of **6** (500 mg, 1.83 mmol) in acetonitrile was added K_2CO_3 (747 mg, 2.3 mmol) under an atmosphere of nitrogen. 5-Bromopent-1-ene (332 mg, 2.22 mmol) was added slowly by syringe. The resulting light-brown solution was stirred at 90 °C for 8 h (TLC monitoring) before the reaction was cooled. The reaction mixture was diluted with ethyl acetate and filtered over Celite with the help of a sintered funnel. The organic layer was concentrated in vacuo and then dissolved in ethyl acetate (30 mL), washed with water and brine, dried ($MgSO_4$) and concentrated in vacuo to yield an oily product. Purification of the crude product by column chromatography (SiO_2; petroleum ether/ethyl acetate, 11:1) gave compound **1c** (490 mg, 78%) as a thick liquid. Yield: 490 mg, 78%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.56–1.70 (m, 2 H), 1.98–2.09 (m, 2 H), 2.43 (s, 3 H), 2.48 (t, J = 2.4 Hz, 1 H), 3.23 (t, J = 7.6 Hz, 2 H), 4.01 (s, 2 H), 4.63 (d, J = 2.4 Hz, 2 H), 4.92–5.07 (m, 2 H), 5.62–5.75 (m, 1 H), 7.29 (d, J = 8.2 Hz, 2 H), 7.73 (d, J = 8.0 Hz, 2 H) ppm. ^{13}C NMR (100.6, $CDCl_3$): δ = 21.6, 27.2, 30.6, 48.1, 52.6, 75.5, 76.9, 115.4, 127.5, 129.6, 136.7, 137.3, 143.5, 168.3 ppm. HRMS (Q-TOF): calcd. for $C_{17}H_{21}NNaO_4S$ $[M + Na]^+$ 358.1089; found 358.1102.

Prop-2-ynyl 2-[*N*-(Hex-5-enyl)-4-methylphenylsulfonamido]acetate (1d): To a solution of **6** (500 mg, 1.83 mmol) in acetonitrile was added K_2CO_3 (770 mg, 5.57 mmol) under an atmosphere of nitrogen. Then, 6-bromohex-1-ene (364 mg, 2.23 mmol) was added slowly by syringe. The resulting light-brown solution was stirred at 90 °C for 8 h (TLC monitoring) before the reaction was cooled. The reaction mixture was diluted with ethyl acetate and filtered over Celite with the help of a sintered funnel. The organic layer was concentrated in vacuo and then dissolved in ethyl acetate (30 mL), washed with water and brine, dried ($MgSO_4$) and concentrated in vacuo to yield an oily product. Purification of the crude product by column chromatography (SiO_2; petroleum ether/ethyl acetate, 12:1) gave compound 1d (500 mg, 76%) as a thick liquid. Yield: 500 mg, 76%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.35–1.45 (m, 2 H), 1.51–1.76 (m, 2 H), 1.91–2.06 (m, 2 H), 2.42 (s, 3 H), 2.49 (t, J = 2.6 Hz, 1 H), 3.25 (t, J = 7.4 Hz, 2 H), 4.09 (s, 2 H), 4.63 (d, J = 2.6 Hz, 2 H), 4.91–5.01 (m, 2 H), 5.68–5.80 (m, 1 H), 7.27 (d, J = 8.1 Hz, 2 H), 7.73 (d, J = 8.1 Hz, 2 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 21.6, 25.8, 27.3, 33.2, 47.8, 48.3, 52.6, 75.4, 76.9, 114.9, 127.6, 129.6, 136.8, 138.3, 143.5, 168.4 ppm. HRMS (Q-TOF): calcd. for $C_{18}H_{24}NO_4S$ $[M + H]^+$ 350.1426; found 350.1434.

But-3-ynyl 2-(*N*-Allyl-4-methylphenylsulfonamido)acetate (9): To a solution of **7** (386 mg, 1.37 mmol) in acetonitrile was added K_2CO_3 (570 mg, 4.12 mmol) under an atmosphere of nitrogen. Allyl bromide (199 mg, 0.2 mL, 1.63 mmol) was added slowly by syringe. The resulting light-brown solution was stirred at 90 °C for 9 h (TLC monitoring) before the reaction was cooled. The reaction mixture was diluted with ethyl acetate and filtered over Celite with the help of a sintered funnel. The combined organic layer was concentrated in vacuo and then dissolved in ethyl acetate (30 mL), washed with water and brine, dried ($MgSO_4$) and concentrated in vacuo to yield an oily product. Purification of the crude product by column chromatography (SiO_2; petroleum ether/ethyl acetate, 9:1) gave compound **9** (419 mg, 95%) as a thick liquid. Yield: 419 mg, 95%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.0 (t, J = 2.6 Hz, 1 H), 2.43 (s, 3 H), 2.45–2.48 (m, 2 H), 3.91 (d, J = 6.6 Hz, 2 H), 4.05 (s, 2 H), 4.13 (t, J = 6.8 Hz, 2 H), 5.12–5.22 (m, 2 H), 5.63–5.74 (m, 1 H), 7.29 (d, J = 8.1 Hz, 2 H), 7.73 (d, J = 8.4 Hz, 2 H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 18.8, 21.6, 46.5, 50.8, 62.8, 70.2, 79.7, 120.1, 127.4, 129.7, 132.3, 136.8, 143.6, 168.7 ppm. HRMS (Q-TOF): calcd. for $C_{16}H_{19}NNaO_4S$ $[M + Na]^+$ 344.0932; found 344.0931.

Allyl 2-[4-Methyl-*N*-(prop-2-ynyl)phenylsulfonamido]acetate (10): To a solution of **8** (300 mg, 1.114 mmol) in acetonitrile was added K_2CO_3 (350 mg, 2.2 mmol) under an atmosphere of nitrogen. Then, 4-bromo-1-butene (195 mg, 0.015 mL, 1.3 mmol) was added slowly by syringe. The resulting light-brown solution was stirred at 90 °C for 8 h (TLC monitoring). The reaction mixture was cooled and diluted with ethyl acetate and then filtered over Celite with the help of a sintered funnel. The organic layer was concentrated in vacuo and then dissolved in ethyl acetate (30 mL), washed with water and brine, dried (Na_2SO_4) and concentrated in vacuo to yield an oily product. Purification of the crude product by column chromatography (SiO_2; petroleum ether/ethyl acetate, 11:1) gave

compound **10** (280 mg, 78%) as a thick liquid. Yield: 280 mg, 78%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.15 (t, J = 2.6 Hz, 1 H), 2.43 (s, 3 H), 4.15 (s, 2 H), 4.26 (d, J = 2.5 Hz, 2 H), 4.58–4.60 (m, 2 H), 5.24–5.34 (m, 2 H), 5.83–5.87 (m, 1 H), 7.30 (d, J = 7.9 Hz, 2 H), 7.72 (d, J = 8.0 Hz, 2 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 21.7, 37.6, 46.9, 66.1, 74.6, 76.5, 119.2, 127.7, 129.8, 131.5, 136.1, 144.1, 168.3 ppm. HRMS (Q-TOF): calcd. for $C_{15}H_{18}NO_4S$ $[M + H]^+$ 308.0957; found 308.0953.

Allyl 2-Amino-2-methylpropanoate–4-Methylbenzenesulfonic Acid (14): To a suspension of AIB **13** (5 g, 48.9 mmol) in benzene (100 mL) was added *p*-toluenesulfonic acid (11.1 g), and reaction mixture was heated at reflux with stirring. The water generated was removed by using a Dean–Stark trap. After complete consumption of **13** (TLC monitoring, 4 h), benzene was removed. The semisolid was taken up in EtOAc and was washed with water; the aqueous layer was extracted with EtOAc (3 × 25 mL). The combined organic layer was washed with brine, dried with Na_2SO_4 and concentrated in vacuo. The product thus obtained was recrystallized from petroleum ether/EtOAc, and the product was obtained as white shiny crystals. Yield: 13.5 g, 87%. M.p. 139–141 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.59 (s, 6 H), 2.37 (s, 3 H), 4.58–4.60 (m, 2 H),5.17–5.30 (m, 2 H), 5.79–5.88 (m, 1 H), 7.14 (d, J = 8.1 Hz, 2 H), 7.78 (d, J = 8.2 Hz, 2 H), 8.33 (s, 3 H) ppm. ^{13}C NMR (100.5 MHz, $CDCl_3$): δ = 21.5, 23.7, 57.4, 66.9, 119.1, 126.3, 128.9, 131.4, 140.5, 141.7, 171.4 ppm.

Allyl 2-Methyl-2-(4-methylphenylsulfonamido)propanoate (15): To a cold solution of **14** (5.0 g, 16 mmol) in DCM was slowly added dry TEA (5.57 g, 57 mmol), and the reaction mixture was stirred at 0 °C. Tosyl chloride (4.0 g, 20 mmol) was added in small portions over a period of 1 h. Stirring was continued at room temperature for 12 h. The solvent was removed and the semisolid was taken up in EtOAc and washed with water. The organic layer was washed with brine, dried with Na_2SO_4 and concentrated in vacuo. The product thus obtained was purified by column chromatography (SiO_2; petroleum ether/ethyl acetate, 19:1) to afford white shiny crystals. Yield: 3.9 g, 82%. M.p. 61–62 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.46 (s, 6 H), 2.42 (s, 3 H), 4.52–4.54 (m, 2 H), 5.24–5.36 (m, 2 H), 5.82–5.90 (m, 1 H), 7.28 (d, J = 8.2 Hz, 2 H), 7.75 (d, J = 8.5 Hz, 2 H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 21.6, 25.8, 59.1, 66.4, 118.9, 127.2, 129.6, 131.5, 139.4, 143.3, 173.8 ppm. HRMS (Q-TOF): calcd. for $C_{14}H_{19}NNaO_4S$ $[M + Na]^+$ 320.0928; found 320.0932.

Allyl 2-Methyl-2-[4-methyl-*N*-(prop-2-ynyl)phenylsulfonamido]propanoate (16): To a solution of **15** (150 mg, 0.5 mmol) in acetonitrile was added K_2CO_3 (200 mg, 1.5 mmol) under an atmosphere of nitrogen. Then, propargyl bromide (100 mg, 0.8 mmol) was added slowly by syringe. The resulting light-brown solution was stirred at 90 °C for 8 h (TLC monitoring) before the reaction was cooled and then quenched by adding ethyl acetate. The reaction mixture was filtered over Celite with the help of a sintered funnel. The organic layer was concentrated in vacuo and then dissolved in ethyl acetate (30 mL), washed with water and brine, dried ($MgSO_4$) and concentrated in vacuo to yield an oily product. Purification of the crude product by column chromatography (SiO_2; petroleum ether/ethyl acetate, 12:1) gave compound **16** (156 mg, 92%) as a thick liquid. Yield: 156 mg, 92%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.27 (s, 6 H), 2.22 (t, J = 2.3 Hz, 1 H), 2.41 (s, 3 H), 4.03 (d, J = 2.3 Hz, 2 H), 4.66–4.69 (m, 2 H), 5.23–5.39 (m, 2 H), 5.91–6.02 (m, 1 H), 7.27 (d, J = 8.3 Hz, 2 H), 7.88 (d, J = 8.2 Hz, 2 H) pm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 21.7, 25.7, 34.5, 63.9, 66.4, 72.9, 80.1, 118.7, 128.3, 129.6, 132.2, 137.5, 143.9, 174.2 ppm. HRMS (Q-TOF): calcd. for $C_{17}H_{22}NO_4S$ $[M + H]^+$ 336.1270; found 336.1282.

General Procedure for CEM–RCM Cascade: To a solution of enyne **1** in dry degassed DCM was added 1,5-hexadiene (3 equiv.) followed by Grubbs' 2nd generation catalyst (20 mol-%) at 30 °C. The reaction mixture was stirred at 30 °C for 6 h (TLC monitoring) and then concentrated in vacuo. Purification of the crude product by column chromatography (SiO_2; petroleum ether/ethyl acetate, 9:1) affords product **2** as thick liquids. Further elution of the column gave **3** as a thick liquid.

Cross-Enyne Metathesis of Enyne 1a: To a solution of enyne **1a** (30 mg, 0.098 mmol) in dry degassed DCM was added 1,5-hexadiene (0.1 mL) followed by Grubbs' 2nd generation catalyst **12** (17 mg, 20 mol-%). The reaction mixture was stirred at 30 °C for 8 h (TLC monitoring) and then concentrated in vacuo. Purification of the crude product by column chromatography (SiO_2; petroleum ether/ethyl acetate, 9:1) afforded product **2a** (17 mg, 47%) as a thick liquid. Further elution of the column gave **3a** (13 mg, 38%) as a thick liquid. Data for **2a**: Yield: 17 mg, 47%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.13–2.26 (m, 4 H), 2.43 (s, 3 H), 3.89 (d, J = 6.4 Hz, 2 H), 4.06 (s, 2 H), 4.69 (s, 2 H), 4.97–5.20 (m, 6 H), 5.63–5.86 (m, 3 H), 6.06 (d, J = 6.5 Hz, 1 H), 7.29 (d, J = 8.2 Hz, 2 H), 7.73 (d, J = 8.3 Hz, 2 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 21.7, 32.5, 33.4, 47.1, 50.9, 64.9, 115.2, 116.3, 120.1, 127.6, 129.6, 129.8, 131.1, 132.3, 136.9, 138.0, 139.8, 143.7, 168.8 ppm. HRMS (Q-TOF): calcd. for $C_{21}H_{27}NNaO_4S$ $[M + Na]^+$ 412.1559; found 412.1562. Data for 3a: Yield: 13 mg, 38%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.17–2.22 (m, 4 H), 2.43 (s, 3 H), 3.89 (d, J = 6.4 Hz, 2 H), 4.06 (s, 2 H), 4.47 (s, 2 H), 5.12–5.22 (m, 2 H), 5.63–5.91 (m, 4 H), 7.29 (d, J = 7.8 Hz, 2 H), 7.76 (d, J = 8.2 Hz, 2 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 21.7, 22.1, 22.2, 47.1, 50.8, 67.5, 120.1, 124.2, 125.9, 127.6, 128.0, 129.8, 130.7, 132.4, 136.9, 143.6, 168.9 ppm. HRMS (Q-TOF): calcd. for $C_{19}H_{23}NNaO_4S$ $[M + Na]^+$ 384.1245; found 384.1256.

Cross-Enyne Metathesis of Enyne 1b: To a solution of enyne **1b** (32 mg, 0.1 mmol) in dry degassed DCM was added 1,5-hexadiene (0.1 mL) followed by Grubbs' 2nd generation catalyst **12** (18 mg, 20 mol-%). The reaction mixture was stirred at 30 °C for 8 h (TLC monitoring) and then concentrated in vacuo. Purification of the crude product by column chromatography (SiO_2; petroleum ether/ethyl acetate, 9:1) afforded product **2b** (18 mg, 47%) as a thick liquid. Further elution of the column gave **3b** (12 mg, 34%) as a thick liquid. Data for **2b**: Yield: 18 mg, 47%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.14–2.19 (m, 4 H), 2.25–2.36 (m, 2 H), 2.41 (s, 3 H), 3.29 (t, J = 7.4 Hz, 2 H), 4.09 (s, 2 H), 4.68 (s, 2 H), 4.96–5.09 (m, 6 H), 5.61–5.82 (m, 3 H), 6.04 (d, J = 16.1 Hz, 1 H), 7.29 (d, J = 8.9 Hz, 2 H), 7.70 (d, J = 8.5 Hz, 2 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 21.7, 32.5, 32.7, 33.5, 47.9, 48.4, 65.0, 115.2, 116.5, 117.5, 127.6, 129.6, 129.7, 131.1, 134.6, 136.9, 138.0, 139.8, 143.6, 168.9 ppm. HRMS (Q-TOF): calcd. for $C_{22}H_{29}NNaO_4S$ $[M + Na]^+$ 426.1715; found 426.1718. Data for **3b**: Yield: 12 mg, 34%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.16–2.19 (m, 4 H), 2.25–2.32 (m, 2 H), 2.42 (s, 3 H), 3.30 (t, J = 7.4 Hz, 2 H), 4.10 (s, 2 H), 4.69 (s, 2 H), 4.99–5.06 (m, 2 H), 5.61–5.67 (m, 4 H), 7.28 (d, J = 8.0 Hz, 2 H), 7.71 (d, J = 8.0 Hz, 2 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 21.7, 32.7, 47.8, 48.1, 48.4, 65.6, 67.2, 117.5, 127.6, 128.3, 128.5, 128.7, 129.8, 131.1, 134.6, 136.9, 143.6, 168.9 ppm. HRMS (Q-TOF): calcd. for $C_{20}H_{25}NNaO_4S$ $[M + Na]^+$ 398.1402; found 398.1363.

Cross-Enyne Metathesis of Enyne 1c: To a solution of enyne **1c** (20 mg, 0.06 mmol) in dry degassed DCM was added 1,5-hexadiene (0.1 mL) followed by Grubbs' 2nd generation catalyst **12** (12 mg, 20 mol-%). The reaction mixture was stirred at 30 °C for 8 h (TLC monitoring) and then concentrated in vacuo. Purification of the

crude product by column chromatography (SiO_2; petroleum ether/ethyl acetate, 9:1) afforded product **2c** (9 mg, 40%) as a thick liquid. Further elution of the column gave 3c (10 mg, 43%) as a thick liquid. Data for 2c: Yield: 9 mg, 40%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.61–1.64 (m, 2 H), 2.0–2.06 (m, 2 H), 2.15–2.20 (m, 4 H), 2.41 (s, 3 H), 3.23 (t, J = 7.3 Hz, 2 H), 4.08 (s, 2 H), 4.75 (s, 2 H), 4.95–5.09 (m, 6 H), 5.62–5.85 (m, 3 H), 6.05 (d, J = 16.1 Hz, 1 H), 7.28 (d, J = 9.0 Hz, 2 H), 7.71 (d, J = 8.3 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.6, 27.1, 30.7, 32.4, 33.4, 47.9, 48.2, 64.9, 115.1, 115.5, 116.3, 127.5, 129.5, 129.6, 130.9, 136.8, 137.4, 137.9, 139.7, 143.5, 168.8 ppm. HRMS (Q-TOF): calcd. for $C_{23}H_{31}NNaO_4S$ [M + Na]$^+$ 440.1872; found 440.1867. Data for **3c**: Yield: 10 mg, 43%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.61–1.67 (m, 2 H), 2.0–2.06 (m, 2 H), 2.11–2.21 (m, 4 H), 2.42 (s, 3 H), 3.23 (t, J = 7.8 Hz, 2 H), 4.07 (s, 2 H), 4.47 (s, 2 H), 4.95 (d, J = 1.2 Hz, 1 H), 5.01 (d, J = 1.4 Hz, 1 H), 5.65–5.90 (m, 4 H), 7.28 (d, J = 8.3 Hz, 2 H), 7.72 (d, J = 8.3 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.6, 21.9, 22.1, 27.1, 30.7, 47.9, 48.2, 67.5, 115.4, 124.2, 125.9, 127.5, 127.9, 129.6, 130.6, 136.8, 137.4, 143.4, 168.9 ppm. HRMS (Q-TOF): calcd. for $C_{21}H_{27}NNaO_4S$ [M + Na]$^+$ 412.1559; found 412.1570.

Cross-Enyne Metathesis of Enyne 1d: To a solution of enyne **1d** (22 mg, 0.063 mmol) in dry degassed DCM was added 1,5-hexadiene (0.1 mL) followed by Grubbs' 2nd generation catalyst **12** (12 mg, 20 mol-%). The reaction mixture was stirred at 30 °C for 8 h (TLC monitoring) and then concentrated in vacuo. Purification of the crude product by column chromatography (SiO_2; petroleum ether/ethyl acetate, 10:1) afforded product **2d** (11 mg, 40%) as a thick liquid. Further elution of the column gave **3d** (9 mg, 35%) as a thick liquid. Data for **2d**: Yield: 11 mg, 40%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.25–1.56 (m, 2 H), 1.95–2.09 (m, 2 H), 2.15–2.21 (m, 6 H), 2.42 (s, 3 H), 3.23 (t, J = 7.5 Hz, 2 H), 4.08 (s, 2 H), 4.69 (s, 2 H), 4.93–5.10 (m, 6 H), 5.63–5.86 (m, 3 H), 6.06 (d, J = 16.5 Hz, 1 H), 7.28 (d, J = 8.3 Hz, 2 H), 7.72 (d, J = 8.3 Hz, 2 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 21.7, 25.8, 27.4, 32.5, 33.5, 45.0, 48.0, 48.3, 64.9, 110.1, 115.2, 116.4, 127.6, 129.6, 129.7, 131.1, 136.9, 138.1, 138.4, 139.8, 143.5, 168.9 ppm. HRMS (Q-TOF): calcd. for $C_{24}H_{34}NO_4S$ [M + H]$^+$ 432.2209; found 432.2216. Data for **3d**: Yield: 9 mg, 35%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.30–1.60 (m, 2 H), 1.90–2.10 (m, 2 H), 2.11–2.25 (m, 6 H), 2.41 (s, 3 H), 3.23 (t, J = 7.2 Hz, 2 H), 4.07 (s, 2 H), 4.68 (s, 2 H), 4.95–5.01 (m, 2 H), 5.65–5.78 (m, 4 H), 7.35 (d, J = 8.2 Hz, 2 H), 7.78 (d, J = 8.0 Hz, 2 H) ppm. HRMS (Q-TOF): calcd. for $C_{22}H_{29}NNaO_4S$ [M + Na]$^+$ 426.1715; found 426.1725.

Cross-Enyne Metathesis of Enyne 10: To a solution of enyne **10** (112 mg, 0.36 mmol) in dry degassed DCM was added 1,5-hexadiene (0.3 mL) followed by Grubbs' 2nd generation catalyst **12** (36 mg, 12 mol-%). The reaction mixture was stirred at 30 °C for 8 h (TLC monitoring) and then concentrated in vacuo. Purification of the crude product by column chromatography (SiO_2; petroleum ether/ethyl acetate, 10:1) afforded product **17** (50 mg, 35%) as a thick liquid. Further elution of the column gave **18** (35 mg, 25%) as a thick liquid. Data for **17**: Yield: 50 mg, 35%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.04–2.17 (m, 4 H), 2.43 (s, 3 H), 4.02 (s, 2 H), 4.12 (s, 2 H), 4.43–4.45 (m, 2 H), 4.93–5.08 (m, 4 H), 5.19–5.29 (m, 2 H), 5.73–5.92 (m, 3 H), 6.01 (d, J = 16.1 Hz, 1 H), 7.29 (d, J = 8.8 Hz, 2 H), 7.72 (d, J = 8.8 Hz, 2 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 21.7, 32.6, 33.4, 46.6, 49.5, 65.8, 115.1, 117.9, 118.9, 127.7, 129.3, 129.7, 131.6, 132.3, 136.8, 138.1, 139.4, 143.6, 168.7 ppm. HRMS (Q-TOF): calcd. for $C_{21}H_{28}NO_4S$ [M + H]$^+$ 390.1739; found 390.1724. Data for **18**: Yield: 35 mg, 25%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.09–2.13 (m, 4 H), 2.43 (s, 3 H), 3.87 (s, 2 H), 4.01 (s, 2 H), 4.46–4.48 (m, 2 H), 5.21–5.29 (m, 2 H), 5.59–5.60 (m, 1 H), 5.77–5.86 (m, 3 H), 7.30 (d, J = 7.9 Hz, 2 H), 7.72 (d, J = 8.4 Hz, 2 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 21.7, 22.1, 22.4, 46.3, 51.8, 65.8, 118.9, 124.6, 126.3, 127.6, 128.3, 129.7, 130.2, 131.7, 137.0, 143.5, 168.7 ppm. HRMS (Q-TOF): calcd. for $C_{19}H_{24}NO_4S$ [M + H]$^+$ 362.1426; found 362.1435.

Cross-Enyne Metathesis of Enyne 9: To a solution of enyne **9** (25 mg, 0.078 mmol) in dry degassed DCM was added 1,5-hexadiene (0.1 mL) followed by Grubbs' 2nd generation catalyst **12** (14 mg, 20 mol-%). The reaction mixture was stirred at 30 °C for 8 h (TLC monitoring) and then concentrated in vacuo. Purification of the crude product by column chromatography (SiO_2; petroleum ether/ethyl acetate, 9:1) afforded product **19** (13 mg, 41%) as a thick liquid. Further elution of the column gave **20** (11 mg, 37%) as a thick liquid. Data for **19**: Yield: 13 mg, 41%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.15–2.22 (m, 4 H), 2.42 (s, 3 H), 2.43–2.47 (m, 2 H), 3.89 (d, J = 6.45 Hz, 2 H), 4.01 (s, 2 H), 4.15 (t, J = 7.3 Hz, 2 H), 4.86–5.15 (m, 4 H), 5.17–5.20 (m, 2 H), 5.63–5.72 (m, 2 H), 5.76–5.86 (m, 1 H), 6.06 (d, J = 16.1 Hz, 1 H), 7.29 (d, J = 8.0 Hz, 2 H), 7.43 (d, J = 8.3 Hz, 2 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 21.7, 31.4, 32.3, 33.6, 47.1, 50.9, 63.9, 115.1, 115.7, 120.0, 127.6, 129.7, 130.1, 132.4, 137.0, 138.1, 141.6, 143.6, 169.0 ppm. HRMS (Q-TOF): calcd. for $C_{22}H_{29}NNaO_4S$ [M + Na]$^+$ 426.1715; found 426.1708. Data for **20**: Yield: 11 mg, 37%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.21–2.38 (m, 4 H), 2.43 (s, 3 H), 2.45–2.49 (m, 2 H), 3.89 (d, J = 6.4 Hz, 2 H), 4.01 (s, 2 H), 4.06 (t, J = 7.42 Hz, 2 H), 5.14–5.19 (m, 2 H), 5.63–5.86 (m, 4 H), 7.29 (d, J = 8.8 Hz, 2 H), 7.73 (d, J = 7.73 Hz, 2 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 21.7, 22.3, 22.4, 34.6, 47.0, 50.8, 64.2, 120.0, 122.8, 127.6, 129.7, 131.9, 132.5, 137.1, 141.6, 143.6, 169 ppm. HRMS (Q-TOF): calcd. for $C_{20}H_{25}NNaO_4S$ [M + Na]$^+$ 398.1402; found 398.1393.

Cross-Enyne Metathesis of Enyne 16: To a solution of enyne **16** (25 mg, 0.075 mmol) in dry degassed DCM was added 1,5-hexadiene (0.1 mL) followed by Grubbs' 2nd generation catalyst **12** (13 mg, 20 mol-%). The reaction mixture was stirred at 30 °C for 8 h (TLC monitoring) and then concentrated in vacuo. Purification of the crude product by column chromatography (SiO_2; petroleum ether/ethyl acetate, 10:1) afforded product **21** (11 mg, 35%) as a thick liquid. Further elution of the column gave **22** (10 mg, 34%) as a thick liquid. Data for **21**: Yield: 11 mg, 35%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.56 (s, 6 H), 2.13–2.15 (m, 4 H), 2.39 (s, 3 H), 4.03 (s, 2 H), 4.67–4.75 (m, 2 H), 4.80 (s, 1 H), 4.96–5.05 (m, 2 H), 5.13 (d, J = 1.4 Hz, 1 H), 5.26–5.31 (m, 1 H), 5.37–5.43 (m, 1 H), 5.56–5.63 (m, 1 H), 5.74–5.84 (m, 1 H), 5.91–6.08 (m, 2 H), 7.22 (d, J = 8.0 Hz, 2 H), 7.77 (d, J = 8.1 Hz, 2 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 21.7, 25.5, 32.6, 33.6, 45.4, 64.5, 66.4, 115.2, 115.3, 118.6, 120.5, 129.1, 129.4, 130.6, 132.4, 137.4, 138.1, 141.3, 143.6, 174.6 ppm. HRMS (Q-TOF): calcd. for $C_{23}H_{32}NO_4S$ [M + H]$^+$ 418.2052; found 418.2037. Data for **22**: Yield: 10 mg, 34%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.59 (s, 6 H), 1.95–2.1 (m, 4 H), 2.42 (s, 3 H), 3.91 (d, J = 2.4 Hz, 2 H), 4.05 (s, 2 H), 4.71–4.73 (m, 2 H), 5.28–5.77 (m, 4 H), 7.25 (d, J = 8.1 Hz, 2 H), 7.81 (d, J = 8.4 Hz, 2 H) ppm. HRMS (Q-TOF): calcd. for $C_{21}H_{27}NNaO_4S$ [M + Na]$^+$ 412.1559; found 412.1552.

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