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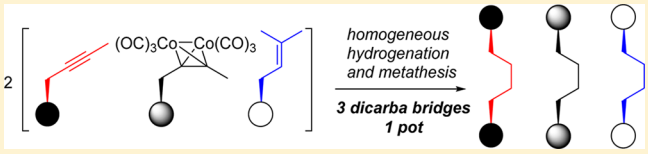
One-Pot Selective Homodimerization/Hydrogenation Strategy for Sequential Dicarba Bridge Formation

James Burnley, W. Roy Jackson, and Andrea J. Robinson*

School of Chemistry, Monash University, Clayton, 3800 Victoria, Australia

Supporting Information

ABSTRACT: The installation of interlocked dicarba bridges into peptide sequences requires the development of a regioselective and chemoselective methodology. This manuscript describes a one-pot, chemoselective synthesis of three 2,7-diaminosuberic acid derivatives from an alkyne, a cobalt−carbonyl protected alkyne, and an alkene using metathesis and homogeneous hydrogenation catalysis.



INTRODUCTION

Disulfide-rich peptides are involved in signaling and include hormones, growth factors, and enzyme inhibitors. They also serve defensive and offensive roles in a wide range of organisms and include microbial defensins, plant cyclotides, and ST enterotoxins. The disulfide bridge in these peptides facilitates the adoption of a well-defined, folded three-dimensional structure. Oxidation of sequence cysteine residues can also reduce conformational flexibility of the peptide, increase selectivity for physiological targets, and reduce susceptibility to enzymatic cleavage.[1] Furthermore, the native, redox-active cystine bridge can also play a major role in receptor activation and cell redox cycling.[2] These features, in addition to a rich array of physiological targets, provide opportunities for the development of new drug leads.

Many venomous creatures immobilize their prey using small, disulfide-rich cyclic peptides bearing highly conserved sequences and disulfide connectivity.[3] The number of disulfide bridges and their arrangement is diverse (Figure 1). The native disulfide bridge can be highly susceptible to reduction, however, and its replacement with metabolically stable motifs is a well-developed approach toward synthetic peptides with enhanced biological properties.[4] In generating structural analogues, however, the disulfide connectivity and three-dimensional topography must be preserved to retain native biological activity. The use of all-carbon bridges as disulfide mimetics is increasing in popularity and can be achieved by prior construction of diaminosuberic acid derivatives and later incorporation into a growing peptide via solid phase peptide synthesis.[5] Alternatively, noncoded olefinic amino acids can be incorporated into a growing peptide sequence and subsequently cross-linked using (olefin) ring-closing metathesis (RCM).[6] Several synthetic dicarba mimetics of native peptides in which one disulfide bridge has been replaced using RCM are known.[7] Regioselective formation of carbon−carbon bonds through chemoselective alkyne cross metathesis (RCAM) has also been described.[8]

The selective formation of multiple, interlocked all-carbon bridges, however, remains a significant challenge. Many species, including spiders, scorpions, and snakes produce potent peptide toxins with greater than three interlocked disulfide bridges (Figure 1).[9] We have previously established a method for the selective introduction of three bridges by chemoselective olefin metathesis.[10,7e] In this manuscript, we describe new methodology using alkyne metathesis (AM) in conjunction with alkene cross metathesis (CM) to facilitate the synthesis of more complex peptide targets (Scheme 1), which together with our previous work, facilitates the selective dicarba replacement of up to five disulfide bridges.

RESULTS AND DISCUSSION

The methodology is demonstrated by the one-pot formation of three 2,7-diaminosuberic acid derivatives (**1**, **2**, and **3**) from an equimolar mixture of alkyne **4**, cobalt−carbonyl protected alkyne **5**, and trisubstituted alkene **6** (Scheme 1). Three commercially available catalysts, Fürstner's (**7**),[11] Wilkinson's (**8**)[12] and Hoveyda−Grubbs' second generation (HGII, **9**),[13] were employed (Scheme 2). For each catalytic transformation, we planned to introduce fresh catalyst to ensure complete conversion, as this is essential when the method is transferred to less reactive, solid-supported peptide substrates. Three different *N*-acyl protecting groups were appended to the three α-substituted glycinate starting materials to ensure that the target diaminosuberic acid products could be isolated and unambiguously characterized (Scheme 1). The final isolation of only three homodimers (**1**−**3**) would be indicative of high chemoselectivity without crossover. Such methodology would then be useful for the solid phase peptide synthesis of multibridged peptides without complication from topoisomer generation.[10,14]

Our previous approach to this problem capitalized on chemoselectivity of alkylidene catalysts toward olefins of

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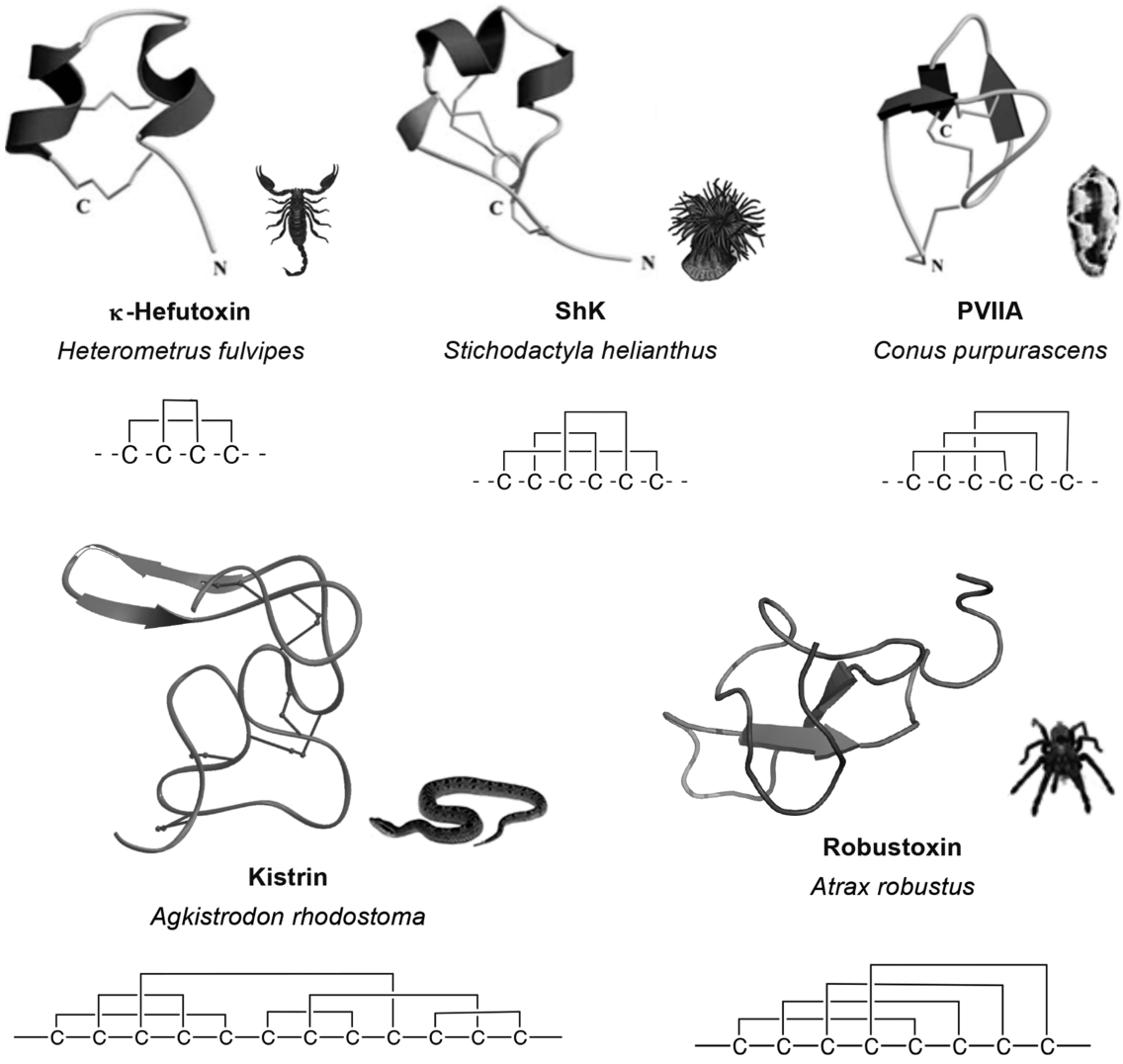

Figure 1. Disulfide-rich peptide venoms.

different steric and electronic character. In this paper, we capitalize on the chemoselectivity of a modern alkyne metathesis catalyst and perform two AM reactions in the presence of olefinic functional groups. The use of transient cobalt−carbonyl protected alkyne **5** facilitates the controlled pairing of the two alkynyl substrates **4** and **5**. Ruthenium alkylidene catalysts, on the other hand, are not chemoselective and facilitate facile enyne metathesis. To prevent deleterious crossover, we planned to reduce each alkyne dimer immediately after its formation; this prevents reaction between **10** and **12** and also eliminates enyne metathesis between alkene **6** and alkynes **10** and **13**. We postulated that the use of highly substituted olefinic substrate **6** would prevent premature hydrogenation and be deprotected by metathesis with ethylene or 2-butene to facilitate the formation of the final dicarba bridge.[10]

Telescopic Construction of Diaminosuberic Acid Derivatives 1, 2, and 3. An equimolar mixture of **4**, **5**, and **6** was prepared and exposed to the eight step reaction sequence outlined in Scheme 3. Construction of the first homodimer **1** began using an AM reaction of alkyne **4**. Optimized conditions for this transformation were employed,[15] which involved the use of Fürstner's catalyst (**7**) and 5 Å molecular sieves to trap the 2-butyne byproduct.[11] This first reaction cycle gave unsaturated *N*-trifluoromethoxy homodimer **10**, which was characterized by low-resolution mass spectrometry (LRMS) and chromatographic analysis. Importantly, unreacted **5** and **6** were also observed without crossover (Scheme 3, reaction i). Decipherable NMR spectra of the mixture, however, could not be obtained at this stage due to the presence of paramagnetic cobalt−carbonyl complex **5**. Next, newly formed acetylenic homodimer **10** was hydrogenated (90 PSI) under optimized reaction conditions using Wilkinson's catalyst (**8**) in THF (Scheme 3, reaction ii).[16] Catalyst **8** was introduced in two portions to minimize poisoning of the catalyst by alkynyl cobalt−carbonyl complex **5**.[17] This procedure resulted in a 1:1 mixture of alkane **1**:olefin **11** (Scheme 3). While incomplete hydrogenation complicated analysis of the reaction mixture, it did not pose any problem to the planned synthesis because the remaining alkene **11** is inert to Fürstner's catalyst (**7**)[18] and can be readily reduced to **1** later in the reaction sequence.

Formation of the second bridge began with decomplexation of cobalt−carbonyl protected alkyne **5** (Scheme 3, reaction iii). This was achieved using ethylenediamine:DCM (1:9) at room temperature for 2 h.[19] The resulting cobalt−ethylenediamine complex was removed from the reaction mixture by aqueous extraction, leaving newly formed, free, monomeric *N*-benzoyl-alkyne **12**. Subsequent AM (Scheme 3, reaction iv) was

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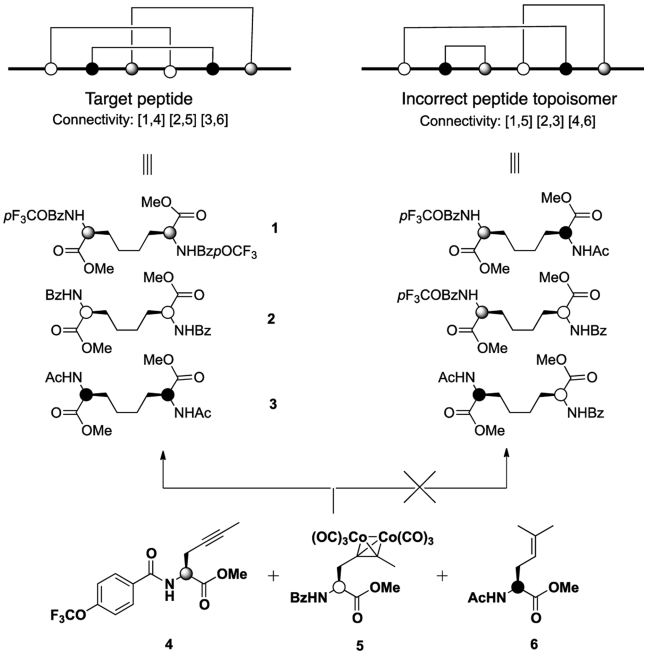
Scheme 1. Regioselective Metathesis to Facilitate Formation of a Target Cyclic Peptide without Formation of Topoisomeric Peptides (1 of 14 Illustrated)



performed to generate the second bridge and generate the unsaturated *N*-benzoyl homodimer **13**. Complete hydrogenation of *N*-benzoyl-homodimer **13** proceeded well with Wilkinson's catalyst (**8**) at a hydrogen pressure of 90 PSI in THF over 18 h, giving saturated diaminosuberic acid derivative **2** (reaction v). This step also completed the reduction of the remaining olefin **11** to the saturated homodimer **1**.

Construction of the final bridge first involved activation of the previously inert prenyl-glycine derivative **6** (Scheme 3, reaction vi). Prenyl-olefin **6** was transformed by CM via butenolysis with *cis*-2-butene and HGII (**9**) in toluene at 75 °C.[10] The resulting crotyl derivative **14** was subjected to homodimerization conditions involving HGII (**9**) in toluene at 40 °C to deliver the third and final unsaturated *N*-acyl-diaminosuberic acid derivative **15**. Because the final step involved hydrogenation, attempts were made to complete this transformation using the Ru-residues from the preceding metathesis step. Unfortunately, this led to an incomplete reaction. However, hydrogenation with Wilkinson's (**8**) catalyst at 90 PSI completed the catalytic sequence and gave the third saturated homodimer **3**. Final separation of the mixture was accomplished using column chromatography to give the target *para*-*N*-trifluoromethoxybenzoyl homodimer **1** (77% yield, 2 steps, 88% per step), *N*-benzoyl homodimer **2** (66% yield, 3 steps, 87% per step), and *N*-acetyl homodimer **3** (68% yield, 3 steps, 81% per step).

CONCLUSIONS

This homogeneous methodology represents an extension to existing methods for the chemoselective formation of multiple carbon−carbon bonds. The methodology presented demonstrates orthogonal reactivity to previously published work, which in combination, could allow for the formation of up to five carbon−carbon bridges in succession. The homogeneous nature of this sequence lends itself to be used in conjunction with solid phase peptide synthesis to tackle complex peptide toxin architecture. Application of this methodology to synthesize dicarba-mimetic peptides is underway.

EXPERIMENTAL SECTION

General Experimental Information. Toluene and THF were distilled from the sodium ketal of benzophenone after heating under reflux for 0.5 h. Toluene was stored over a potassium mirror. Dichloromethane was distilled from CaH_2 after heating under reflux for 0.5 h. Light petroleum refers to the fraction with bp 40−60 °C. Molecular sieves of 5 Å were dried by heating at 500 °C for 0.5 h under high vacuum. Analytical thin-layer chromatography was carried out using aluminum backed plates coated with silica and visualized under UV light (at 254 nm), aqueous basic $KMnO_4$, or acidified vanillin in ethanol. Flash chromatography was carried out using silica 60 Å with the specified eluent.

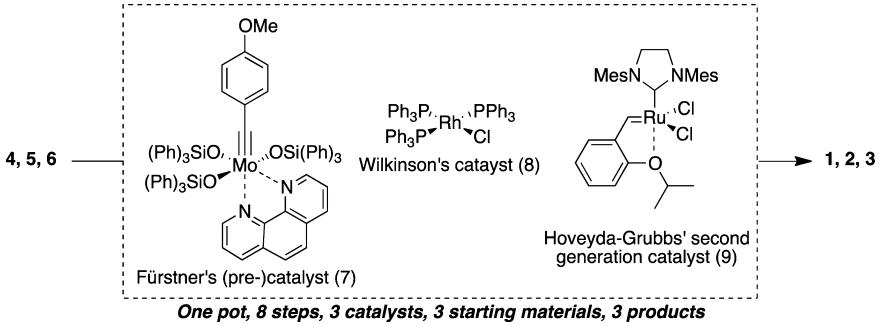
All experiments involving metathesis were prepared in a drybox under nitrogen with an oxygen concentration of <10 ppm as measured by an oxygen sensor, all further manipulations were carried out with standard Schlenk techniques using nitrogen as the inert atmosphere.

Hydrogenation experiments were performed with a Fischer−Porter tube using purchased high purity hydrogen at a pressure of 90 PSI.

Infrared spectra (IR) were recorded neat. IR absorptions (υ_{max}) are reported in wavenumbers (cm^{-1}) with the relative intensities expressed as s (strong), m (medium), w (weak), or prefixed b (broad). ^1H and ^{13}C NMR spectra were recorded at 300 or 400 MHz as solutions in deuterated solvents as specified. Chemical shifts are quoted in parts per million (ppm) and are referenced according to residual solvent peaks. Coupling constants, *J*, quoted in Hz, are quoted to the nearest 0.5 Hz due to an applied spectrometer line broadening of 0.3 Hz. Multiplicity is expressed as singlet (s), doublet (d), triplet (t), quartet (q), apparent quintet (app q), or multiplet (m), or in combination with the prefix (br) used to describe broadening, if necessary.

Low (QMS-quadrupole) and high (LC-TOF) resolution electrospray ionization (ESI) mass spectra were recorded as solutions in specified solvents. Spectra were recorded in positive and negative modes (ESI^+ and ESI^-) as specified. The mass spectrometer was

Scheme 2. Metathesis Substrates 4, 5, and 6, 2,7-Diaminosuberic Acid Derivatives 1, 2, and 3, and Catalysts 7, 8, and 9



One pot, 8 steps, 3 catalysts, 3 starting materials, 3 products

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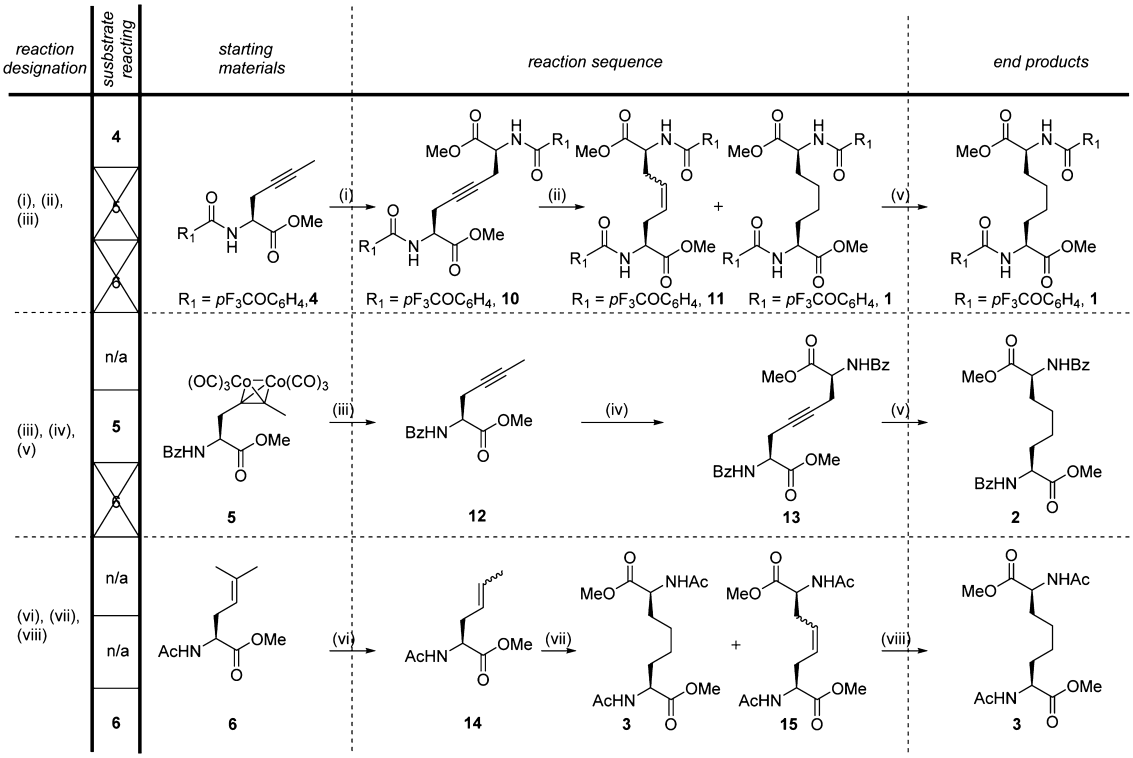
Scheme 3. Telescoped Sequence for the Chemoselective Formation of Three Carbon−Carbon Bridges[a]



[a]Reagents and conditions. 1st Dimerization: (i) Fürstner's catalyst (**7**) (10 mol %), $MnCl_2$ (1:1, w/w), 5 Å sieves, toluene, 80 °C → rt, 4 h; (ii) Wilkinson's catalyst (**8**) (10 mol %), 90 PSI H_2, THF, rt, 2 × 1 h. 2nd Dimerization: (iii) ethylenediamine:DCM (1:9), 2 h, rt; (iv) Fürstner's catalyst (**7**) (10 mol %), $MnCl_2$ (1:1, w/w), 5 Å sieves, toluene, 80 °C → rt, 4 h; (v) Wilkinson's catalyst (**8**) (10 mol %), 90 PSI H_2, THF, rt, 18 h. 3rd Dimerization: (vi) HGII (**9**) (5 mol %), *cis*-2-butene, toluene 75 °C, 18 h; (vii) HGII (**9**) (5 mol %), toluene 40 °C, 18 h, then H_2 (90 PSI) 18 h, THF; (viii) Wilkinson's catalyst (**8**) (10 mol %), 90 PSI H_2, THF, rt, 18 h.

calibrated with an internal standard solution of sodium iodide in MeOH.

Optical activity was measured as solutions in chloroform.

*(S)-Methyl 2-(4-(Trifluoromethoxy)benzamido)hex-4-ynoate (**4**).* TMSCl (0.72 mL, 5.64 mmol) was added to MeOH (10 mL) at room temperature, and the mixture was stirred for 0.5 h. (*S*)-2-Amino-4-hexynoic acid (359 mg, 2.82 mmol) was added in one portion, and the resulting mixture was heated at reflux for 1 h. After 1 h, the methanol was distilled off to give a colorless residue, which was placed under high vacuum for 2 h.

DCM (10 mL) and triethylamine (0.78 mL, 5.64 mmol) were added to the residue, and the suspension was cooled to 0 °C. 4-(Trifluoromethoxy)benzoyl chloride (0.53 mL, 3.38 mmol) was then added dropwise over 1 min, and the mixture was allowed to warm to room temperature over 0.5 h. The subsequent mixture was stirred for a further 18 h, at which point aqueous hydrochloric acid (20 mL, 1 M) was added. The product was extracted with DCM (3 × 50 mL) and dried with sodium sulfate, and the solvent was removed in vacuo to give a pale yellow residue. The resulting residue was purified via flash column chromatography (5% ethyl acetate-light petroleum) to give title compound **4** as a colorless crystalline solid (855 mg, 92%).

$[\alpha]_D^{22}$ +101 (*c* 0.89, $CHCl_3$); ν_{max} (ATR) 3392 (NH, br), 1744 (C═O ester, s), 1655 (C═O, amide s), 1515 (m), 1217 (s), 743 (s); δ_H (300 MHz, $CDCl_3$) 7.90−7.85 (m, 2H), 7.30−7.26 (m, 2H), 6.91 (d, *J* = 8.0 Hz, 1H), 4.87 (dt, *J* = 8.0 Hz, 4.5 Hz, 1H), 3.80 (s, 3H), 2.81 (dq, *J* = 4.5 Hz, 2.5 Hz, 2H), 1.80 (s, 3H); δ_C (100 MHz, $CDCl_3$) 171.5, 166.0, 152.0, 132.7, 129.4, 121.5, 121.0 (q, J_{CF} = 258 Hz), 79.9, 73.1, 53.2, 51.8, 23.1, 3.9; δ_F (400 MHz, $CDCl_3$) −57.7; HRMS ESI calcd for $C_{15}H_{15}F_3NO_4$ $[M + H]^+$ 330.0948, found 330.0943; calcd for $C_{15}H_{14}F_3NNaO_4$ $[M + Na]^+$ 352.0767, found 352.0766.

*Cobalt−Carbonyl Protected (S)-Methyl 2-Benzamidohex-4-ynoate (**5**). Part 1: (S)-Methyl 2-benzamidohex-4-ynoate (**12**).* TMSCl (0.71 mL, 5.60 mmol) was added to MeOH (30 mL) at room temperature, and the mixture was stirred for 30 min. (*S*)-2-Amino-4-hexynoic acid (356 mg, 2.79 mmol) was added in one portion, and the resulting mixture was heated at reflux for 1 h. After 1 h, the methanol was distilled off to give a colorless residue, which was placed under high vacuum for 2 h.

The residue was suspended in DCM (10 mL), and triethylamine was added (0.78 mL, 5.64 mmol); then, the mixture was cooled to 0 °C. Benzoyl chloride (0.40 mL, 3.38 mmol) was added dropwise over 1 min, and the mixture was allowed to warm to room temperature over 0.5 h. The subsequent mixture was stirred for a further 18 h. Aqueous hydrochloric acid (20 mL, 1 M) was added; the product was extracted with DCM (3 × 50 mL) and dried with sodium sulfate, and the solvent was removed in vacuo to give a pale yellow residue. The resulting residue was purified via flash column chromatography (20% ethyl acetate-light petroleum) to give (*S*)-methyl 2-benzamidohex-4-ynoate (**12**) as a colorless crystalline solid (618 mg, 90%).

$[\alpha]_D^{22}$ +122 (*c* 0.82, $CHCl_3$); ν_{max} (ATR) 3302 (NH, br), 1730 (C═O ester, s), 1631 (C═O amide, s), 1534 (s), 1185 (s), 684 (s); δ_H (300 MHz, $CDCl_3$) 7.83−7.80 (m, 2H), 7.54−7.41 (m, 3H), 6.95 (br d, *J* = 8.5 Hz, 1H), 4.88 (dt, *J* = 8.5 Hz, 5.0 Hz, 1H), 3.79 (s, 3H), 2.80 (dq, *J* = 5.0 Hz, 2.5 Hz, 2H), 1.75 (t, *J* = 2.5 Hz, 3H); δ_C (75 MHz, $CDCl_3$) 171.6, 167.2, 134.2, 132.1, 128.9, 127.4, 79.7, 73.2, 53.0, 51.7, 23.1, 3.8; HRMS ESI calcd for $C_{14}H_{15}NNaO_3$ $[M + Na]^+$ 268.0944, found 268.0945.

*Part 2: Cobalt−Carbonyl Protected (S)-Methyl 2-Benzamidohex-4-ynoate (**5**).* (*S*)-Methyl 2-benzamidohex-4-ynoate (**12**) (200 mg, 0.81 mmol) was dissolved in DCM (2 mL); then, dicobalt octacarbonyl (290 mg, 0.85 mmol) was added, and the red/brown mixture was stirred for 18 h. The solvent was then removed in vacuo. The resulting residue was purified via flash column chromatography (10% ethyl acetate-light petroleum) to give title compound **5** as a deep red/brown oil (425 mg, 98%). The title compound was found to be

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stable for a week under nitrogen at −20 °C. However, decomposition was observed when stored at ambient temperature or under air.

$[\alpha]_D^{22}$ +105 (*c* 0.02, $CHCl_3$); ν_{max} (ATR) 3522 (br, NH), 2087 (m, CO), 2044 (s, CO), 1995 (br, CO), 1740 (C═O ester, m), 1639 (C═O amide, m), 1101; δ_H (300 MHz, $CDCl_3$) 7.84−7.81 (m, 2H), 7.71−7.46 (m, 3H), 6.91 (m, 1H), 5.01 (m, 1H), 3.86 (s, 3H), 3.76 (d, *J* = 13.0 Hz, 1H), 3.47 (d, *J* = 13.0 Hz, 1H), 1.25 (s, 3H); HRMS ESI calcd for $C_{20}H_{15}Co_2NNaO_9$ $[M + Na]^+$ 553.9303, found 553.9298. A low resolution mass spectrum could not be obtained.

(S)-Methyl 2-Acetamido-5-methylhex-4-enoate (6).[10] *Part 1: (S)-Methyl 2-Acetamidopent-4-enoate.* TMSCl (2.20 mL, 1.73 mmol) was added to MeOH (15 mL) at room temperature, and the mixture was stirred for 30 min. (*S*)-2-Amino-4-pentenoic acid (1.00, 8.66 mmol) was added, and the mixture was then heated at reflux for 1 h. After 1 h, the methanol was distilled off to give an oily residue, which was placed under high vacuum for 2 h.

Next, DCM (15 mL) was added, and the suspension was cooled to 0 °C. Triethylamine (3.02 mL, 21.7 mmol) and acetic anhydride (0.85 mL, 8.69 mmol) were added sequentially, and the mixture was warmed to room temperature for 2 h. Aqueous hydrochloric acid (10 mL, 1 M) was added; the product was extracted with DCM (3 × 50 mL), and the combined organic phase was dried with sodium sulfate. The solvent was removed in vacuo to give a pale yellow oil. The resulting oil was purified via flash column chromatography (ethyl acetate) to give (*S*)-methyl 2-acetamidopent-4-enoate as a colorless, viscous oil (1.26 g, 85%).

$[\alpha]_D^{22}$ +45.9 (*c* 0.75, $CHCl_3$; lit.[10] +45.0); ν_{max} (ATR) 3279 (NH, br), 1740 (C═O ester, s), 1651 (C═O amide, s), 1537 (s), 1200 (s), 1147 (s); δ_H (300 MHz, $CDCl_3$) 6.10 (br d, *J* = 8.0 Hz, 1H), 5.69−5.62 (m, 1H), 5.12 (m, 1H), 5.09−5.07 (m, 1H), 4.69−4.64 (m, 1H), 3.72 (s, 3H), 2.56−2.47 (m, 2H), 1.99 (s, 3H); δ_C (75 MHz, $CDCl_3$) 127.6, 107.0, 132.5, 119.4, 52.7, 52.0, 36.8, 23.4; HRMS ESI calcd for $C_8H_{13}NNaO_3$ $[M + Na]^+$ 194.0788, found 194.0787.

Part 2: (S)-Methyl 2-Acetamido-5-methylhex-4-enoate (6). (*S*)-Methyl 2-acetamidopent-4-enoate (7 mg, 4.38 mmol) and Hoveyda−Grubbs second generation catalyst (137 mg, 0.22 mmol) were dissolved in toluene (3 mL); the mixture was cooled (∼ −296 °C), and a partial vacuum was applied. Isobutylene (∼1 mL) was condensed into the reaction mixture, and the mixture was carefully heated to 60 °C for 16 h. The resulting brown mixture was cooled to room temperature and vented, and the remaining gas was removed under a flow of nitrogen. The solvent was then removed in vacuo to give a brown semisolid. The resulting solid was purified via flash column chromatography (50% ethyl acetate-light petroleum) to give (*S*)-Methyl 2-acetamido-5-methylhex-4-enoate **6** as a gray crystalline solid (480 mg, 55%).

$[\alpha]_D^{22}$ +58.8 (*c* 0.25, $CHCl_3$; lit.[10] +58.2); ν_{max} (ATR) 3279 (NH, br), 1740 (C═O ester, s), (1651 (C═O amide, s), 1537 (s), 1200 (s), 1147 (s); δ_H (300 MHz, $CDCl_3$) 6.10 (br d, *J* = 6.0 Hz, 1H), 4.99−4.97 (m, 1H), 4.62 (ddd, *J* = 8.0 Hz, 6.0 Hz, 2.5 Hz, 1H), 3.72 (s, 3H), 2.45−2.43 (m, 1H), 2.41−2.39 (m, 1H), 2.97 (s, 3H), 1.69 (s, 3H), 1.58 (s, 3H); δ_C (75 MHz, $CDCl_3$) 173.0, 170.0, 136.8, 117.8, 52.6, 52.4, 31.0, 26.2, 23.5, 18.2; HRMS ESI calcd for $C_{10}H_{17}NNaO_3$ $[M + Na]^+$ 222.1101, found 222.1103.

(2S,7S)-Dimethyl 2,7-Bis(benzamido)oct-4-ynedioate (13). See Figure S1 for detailed procedures and tabulated results for the optimization of AM reactions.

$[\alpha]_D^{22}$ +106 (*c* 0.07, $CHCl_3$); ν_{max} (ATR) 3393 (NH, br), 1744 (C═O ester, s), 1655 (C═O amide, s), 1515 (s), 1214 (s), 713 (s); δ_H (300 MHz, $CDCl_3$) 8.02−8.00 (m, 4H), 7.56 (d br, *J* = 8.0 Hz, 2H), 7.52−7.41 (m, 6H), 5.02−4.98 (m, 2H), 3.47 (s, 6H), 2.77 (br q, *J* = 17.5 Hz, 4H); δ_C (75 MHz, $CDCl_3$) 172.3, 167.3, 133.8, 132.1, 128.6, 128.0, 78.4, 53.0, 51.6, 23.7; HRMS ESI calcd for $C_{24}H_{25}N_2O_6$ $[M + H]^+$ 437.1707, found 437.1740; calcd for $C_{24}H_{24}N_2NaO_6$ $[M + Na]^+$ 459.1527, found 459.1524.

See Figure S2 for detailed procedures and results for the optimization of reduction and deprotection of **4** and **5**.

See Figure S4 for the examination of the chemoselectivity of Fürstner's catalyst.

Procedures for the Telescoped Chemoselective Reaction Series. Performed on 0.20 mmol scale of **4**, **5**, and **6**. The reaction was assessed by low resolution mass spectrometry of the crude reaction mixture after work up; the relevant ions are listed below the procedures.

*Step 1: First Alkyne Dimerization (**4** + **5** + **6** → **10** + **5** + **6**).* Anhydrous manganese dichloride (25.0 mg) and Fürstner's catalyst (**7**) (25.0 mg, 0.02 mmol) in toluene (4 mL, 0.05 M) were heated at 80 °C for 30 min to give a brown/green solution. In a drybox, the catalyst solution was added to (*S*)-methyl 2-(4-(trifluoromethoxy)-benzamido)hex-4-ynoate (**4**) (65.9 mg, 0.20 mmol), cobalt−carbonyl protected (*S*)-methyl 2-benzamidohex-4-ynoate (**5**) (106 mg, 0.20 mmol), (*S*)-methyl 2-acetamido-5-methylhex-4-enoate (**6**) (39.9 mg, 0.20 mmol), and 5 Å sieves (100 mg) in toluene (1 mL). The resulting mixture was stirred at room temperature for 4 h. The solvent was evaporated in vacuo, and the residue was dissolved in ethyl acetate (2 mL) and filtered through Celite (washing with 10 × 2 mL MeOH). The solution was concentrated in vacuo and used immediately in the next step.

LRMS ESI calcd for $C_{26}H_{22}F_6N_2NaO_8$ $[M + Na]^+$ 627.1, found 627.1 (**10**); calcd for $C_{10}H_{17}NNaO_3$ $[M + Na]^+$ 222.2, found 222.2 (**6**). Cobalt−carbonyl complex **5** is not observable by low resolution ESI mass spectrometry.

*Step 2: First Alkyne Reduction (**10** + **5** + **6** → **1** + **5** + **6** + **11**).* In a drybox, Wilkinson's catalyst **8** (18.5 mg, 0.02 mmol) was added to the crude reaction mixture of **10**, **5**, and **6** from the previous step (0.20 mmol) and dissolved in THF (2 mL) in a Fisher−Porter tube. Hydrogen was introduced via 3 purge refill cycles (−20 to 90 PSI), and a final pressure of 90 PSI was retained for 1 h. The hydrogen was vented; the mixture was concentrated in vacuo and redissolved in THF (2 mL). Another portion of Wilkinson's catalyst (18.5 mg, 0.02 mmol) was added, and hydrogen was reintroduced via 3 purge refill cycles (−20 to 90 PSI) to a final pressure of 90 PSI, which was maintained for another 1 h. After venting, the solvent was then evaporated in vacuo, and the residue was dissolved in ethyl acetate (2 mL) and filtered through Celite (washing with 10 × 2 mL MeOH). The solution was concentrated in vacuo and used immediately in the next step.

LRMS ESI calcd for $C_{26}H_{24}F_6N_2NaO_8$ $[M + Na]^+$ 629.1, found 629.2 (**11**); calcd for $C_{26}H_{26}F_6N_2NaO_8$ $[M + Na]^+$ 631.1, found 630.2 (**1**); calcd for $C_{10}H_{17}NNaO_3$ $[M + Na]^+$ 222.2, found 222.3 (**6**). Cobalt−carbonyl complex **5** is not observable by low resolution ESI mass spectrometry.

*Step 3: Alkyne Deprotection (**1** + **5** + **6** + **11** → **1** + **6** + **11** + **12**).* Ethylenediamine:DCM (10 mL, 1:9) was added to the crude reaction mixture containing **1**, **5**, **6**, and **11** from the previous step (0.20 mmol), and the resulting solution was stirred for 3 h. Water (10 mL) was added to the mixture, and the biphasic solution was stirred for 1 h. The mixture was extracted with DCM (3 × 10 mL), and the combined extracts were washed with brine (10 mL). The resulting organic solvent was dried with sodium sulfate, evaporated in vacuo, and used immediately in the next step.

LRMS ESI calcd for $C_{26}H_{24}F_6N_2NaO_8$ $[M + Na]^+$ 629.1, found 629.0 (**11**); calcd for $C_{26}H_{26}F_6N_2NaO_8$ $[M + Na]^+$ 631.1, found 631.0 (**1**); calcd for $C_{14}H_{15}NNaO_3$ $[M + Na]^+$ 268.3, found 268.1 (**12**); calcd for $C_{10}H_{17}NNaO_3$ $[M + Na]^+$ 222.2, found 222.2 (**6**).

*Step 4: Second Alkyne Dimerization (**1** + **6** + **11** + **12** → **1** + **6** + **11** + **13**).* Anhydrous manganese dichloride (25.0 mg) and Fürstner's catalyst (**7**) (25.0 mg, 0.02 mmol) in toluene (2 mL, 0.10 M) were heated at 80 °C for 30 min to give a brown/green solution. In a drybox, the catalyst solution was added to the crude reaction mixture containing **1**, **6**, **11**, and **13** from the previous step (0.2 mmol) and 5 Å sieves (100 mg) in toluene (1 mL). The resulting mixture was stirred at room temperature for 18 h. The solvent was evaporated in vacuo, and the residue was dissolved in ethyl acetate (2 mL) and filtered through Celite (washing with 10 × 2 mL MeOH). The solution was concentrated in vacuo and used immediately in the next step.

LRMS ESI calcd for $C_{26}H_{24}F_6N_2NaO_8$ $[M + Na]^+$ 629.1, found 629.0 (**11**); calcd for $C_{26}H_{26}F_6N_2NaO_8$ $[M + Na]^+$ 631.1, found 631.0

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(**1**); calcd for $C_{24}H_{24}N_2NaO_6$ $[M + Na]^+$ 459.4, found 459.1 (**13**); calcd for $C_{10}H_{17}NNaO_3$ $[M + Na]^+$ 222.2, found 222.2 (**6**).

*Step 5: Reduction of Alkyne Dimer **13** and Remaining Olefin **11** (**1** + **6** + **11** + **13** → **1** + **2** + **6**).* In a drybox, Wilkinson's catalyst (18.5 mg, 0.02 mmol) was added to the crude reaction mixture containing **1**, **6**, **11**, and **13** from the previous step (0.20 mmol) and dissolved in THF (2 mL) in a Fisher−Porter tube. Hydrogen was introduced via 3 purge refill cycles (−20 to 90 PSI), and a final pressure of 90 PSI was maintained for 4 h. After venting, the solvent was then evaporated in vacuo, and the residue was dissolved in ethyl acetate (2 mL) and filtered through Celite (washing with 10 × 2 mL MeOH). The solution was concentrated in vacuo and used immediately in the next step.

LRMS ESI calcd for $C_{26}H_{26}F_6N_2NaO_8$ $[M + Na]^+$ 631.1, found 631.1 (**1**); calcd for $C_{24}H_{28}N_2NaO_6$ $[M + Na]^+$ 463.5, found 463.2 (**2**); calcd for $C_{10}H_{17}NNaO_3$ $[M + Na]^+$ 222.2, found 222.3 (**6**).

*Step 6: Activation of Prenyl Glycine **6** (**1** + **2** + **6** → **1** + **2** + **14**).* The crude reaction mixture containing **1**, **2**, and **6** from the previous step was dissolved in toluene (3 mL), and Hoyveda−Grubbs second generation catalyst (12.5 mg, 0.02 mmol) was added. The flask was cooled (∼ −296 °C) and placed under partial vacuum; *cis*-2-butene (∼1 mL) was condensed into the mixture, and the sealed tube was then carefully heated at 40 °C for 18 h. The mixture was then cooled and vented, and the remaining gas was removed under a stream of nitrogen. The organic solvent was evaporated in vacuo, and the residue was dissolved in ethyl acetate (1 × 2 mL) and filtered through Celite (washing with 10 × 2 mL MeOH). The solution was concentrated in vacuo and used immediately in the next step.

LRMS ESI calcd for $C_{26}H_{26}F_6N_2NaO_8$ $[M + Na]^+$ 631.1, found 631.0 (**1**); calcd for $C_{24}H_{28}N_2NaO_6$ $[M + Na]^+$ 463.5, found 463.0 (**2**); calcd for $C_9H_{15}KNO_3$ $[M+K]^+$ 224.1, found 224.2 (**14**).

*Steps 7 and 8: Alkene Dimerization and Tandem Reduction (**1** + **2** + **14** → **1** + **2** + **3** + **15**).* Hoyveda−Grubbs second generation catalyst (12.5 mg, 0.02 mmol) and toluene (2 mL) were added sequentially to the crude reaction product containing **1**, **2**, and **14** from the previous step, and the mixture was heated at 40 °C for 18 h. The crude mixture containing **1**, **2**, and **15** was then cooled and transferred to a Fischer−Porter tube containing methanol (2 mL). Hydrogen was introduced via 3 purge refill cycles (−20 to 45 PSI), and a final pressure of 90 PSI was maintained for 18 h. After venting, the solvent was then evaporated in vacuo, and the residue was dissolved in ethyl acetate (2 mL) and filtered through Celite (washing with 10 × 2 mL MeOH).

The resulting residue was then subjected to column chromatography (neat petrol to ethyl acetate to 10% MeOH:DCM) to give the following products in order of elution:

*(2S,7S)-Dimethyl 2,7-Bis(benzamido)octanedioate (**2**).*[10] Colorless crystalline solid (29 mg, 66%); $[\alpha]_D^{22}$ +33.0 (*c* 0.12, $CHCl_3$); ν_{max} ($CHCl_3$) 3311 (NH, br), 1735 (C═O ester, s), 1633 (C═O amide, s), 1523, 1215, 1174; δ_H (400 MHz, $CDCl_3$) 7.80−7.78 (m, 4H), 7.50−7.48 (m, 2H), 7.37−7.33 (m, 4H), 6.77 (br d, *J* = 7.0 Hz, 2H), 4.83−4.78 (m, 2H), 3.77 (s, 6H), 1.97−1.82 (m, 2H), 1.79−1.72 (m, 2H), 1.51−1.47 (m, 2H), 1.42−1.36 (m, 2H); δ_C (100 MHz, $CDCl_3$) 173.4, 167.4, 134.2, 132.1, 129.0, 127.4, 52.4, 52.7, 32.7, 25.1; HRMS ESI calcd for $C_{24}H_{28}N_2NaO_6$ $[M + Na]^+$ 463.1840, found 463.1842.

*(2S,7S)-Dimethyl 2,7-Bis(4-(trifluoromethoxy)benzamido)-octanedioate (**1**).* Pale yellow crystalline solid (47 mg, 77%); $[\alpha]_D^{22}$ +11.5 (*c* 0.31, $CHCl_3$); ν_{max} ($CHCl_3$) 3298 (NH, br), 1734 (C═O ester, s), 1635 (C═O amide, s), 1255 (CF, s), 1206 (CF, s), 1149 (CF, s); δ_H (400 MHz, $CDCl_3$) 7.84−7.81 (m, 4H), 7.24−7.22 (m, 4H), 6.86 (br d, *J* = 7.0 Hz, 2H), 4.81−4.76 (m, 2H), 3.77 (s, 6H), 1.98−1.85 (m, 2H), 1.82−1.78 (m, 2H), 1.54−1.51 (m, 2H), 1.49−1.42 (m, 2H); δ_C (100 MHz, $CDCl_3$) 173.3, 166.1, 152.0, 132.5, 129.4, 121.9, 120.0 (q, J_{CF} = 260 Hz), 50.9, 52.7, 32.5, 25.0; δ_F (400 MHz, $CDCl_3$) −57.8; HRMS ESI calcd for $C_{26}H_{26}F_6N_2NaO_8$ $[M + Na]^+$ 631.1486, found 631.1487.

*(2S,7S)-Dimethyl 2,7-Diacetamidooctanedioate (**3** + **15**).* Brown oil (22 mg, 68% total yield, ∼4(**3**):1(**15**)); ν_{max} ($CHCl_3$) 3275 (NH, br), 1736 (ester C═O, s), 1650 (C═O amide, s), 1294, 1460, 1170; δ_H (400 MHz, $CDCl_3$) 6.48 (br d, *J* = 8.0 Hz, 2H, observable peaks for olefinic contamination), 6.26 (br d, *J* = 7.0 Hz, 2H), 5.38−5.36 (m, 2H, observable peaks for olefinic contamination), 4.69−4.64 (m, 2H, observable peaks for olefinic contamination), 4.59−4.53 (m, 2H), 3.74 (s, 6H, observable peaks for olefinic contamination), 3.72 (s, 6H), 2.01 (s, 6H, observable peaks for olefinic contamination), 2.00 (s, 6H), 1.84−1.74 (m, 2H), 1.71−1.61 (m, 2H), 1.40−1.24 (m, 4H); δ_C (100 MHz, $CDCl_3$) 173.3, 170.3, 128.9 (observable peaks for olefinic contamination), 52.7, 52.2, 32.4, 24.9, 23.4; HRMS ESI calcd for $C_{14}H_{24}N_2NaO_6$ $[M + Na]^+$ 339.1527, found 339.1530; calcd for $C_{14}H_{22}N_2NaO_6$ $[M + Na]^+$ 337.1370, found 337.1375.

*Reduction of the Mixture of **3** and **15** by Wilkinson's Catalyst.* The mixture containing **3** and **15** (22 mg, 69.8 μmol) was dissolved in THF:MeOH (10:1, 1 mL) in a Fischer−Porter tube; then, Wilkinson's catalyst was added (6 mg, 6.98 μmol). Hydrogen was introduced via 3 purge refill cycles (−20 to 90 PSI), and a final pressure of 90 PSI was retained for 8 h. After venting, the solvent was then evaporated in vacuo to give a residue, which was subjected to column chromatography (neat petrol to ethyl acetate to 10% MeOH:DCM) to give **3** as a pale brown oil (21 mg, 95%). All data matched that reported previously.[10]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01312.

Detailed assessment and NMR analysis of screening reactions and electronic copies of the carbon and proton NMR spectra for compounds **1**−**6**, **12**, and **13** (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: Andrea.robinson@monash.edu. Fax: 61 03 9905 4597. Tel: 61 03 9905 4553.

Notes

The authors declare no competing financial interest.

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(16) Conditions were established to facilitate alkyne reduction without concomitant decomplexation of the cobalt−carbonyl protected alkyne **5**. Diazene and Pd(0)-catalyzed hydrogenation with formic acid led to poor conversion and premature decomplexation, respectively. Competition studies involving hydrogenation using Wilkinson's catalyst under varying solvent conditions were conducted (see Figure S2). The reaction rate was slow in neat DCM, and DCM-MeOH mixtures resulted in concomitant Co-complex decomposition. Optimized conditions were used in the telescopic sequence employing THF as the reaction solvent.
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