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Alkynyl β-sheet peptidomimetics retain their anti-parallel sheet conformation when coordinated to tungsten

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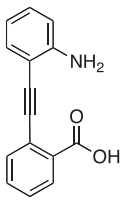
ABSTRACT

Peptide derivatives (**8** and **9**) of 2-amino-2′-carboxydiphenylacetylene (**1**) were prepared using the Sonogashira reaction and standard peptide chemistry. As reported earlier by Kemp and Li (Ref. [1]), **8** and **9** adopt anti-parallel β-sheet conformations in solution. Reaction of **8** and **9** with $W(CO)_3(dmtc)_2$ produced the tungsten mono-alkyne complexes **10** and **11** as a mixture of two inseparable diastereomers (**10a** and **10b**, and **11a** and **11b**) resulting from two different spatial arrangements of the dmtc ligands. The respective mixtures of the two diastereomers were characterized by ES-MS and ^1H NMR spectroscopy. The solution conformations of the diastereomers were probed using NOESY and DMSO titration experiments. The data from these experiments show that the peptide portions of **10** and **11** maintain their anti-parallel β-sheet conformations following coordination to tungsten.

Introduction

In 1995 Kemp and Li reported the synthesis of 2-amino-2′-carboxyphenylacetylene (**1**), the synthesis of peptide derivatives incorporating **1** (shown generally as structure **2**), and the conformational analysis of the peptide derivatives [1,2]. As they had hypothesized, the diphenylacetylene moiety constrained these peptide derivatives (like **2**) to an anti-parallel β-sheet conformation. In subsequent work Spivey and co-workers have incorporated **1** into a peptide designed to mimic a domain in human IgE [3]. The key structural element in **2** is the acetylene group, which positions the amide NH and C=O in a position where they can form an intramolecular hydrogen bond leading to adoption of the anti-parallel β-sheet conformation.



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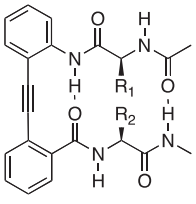

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In recent work our group has been developing methods to use organometallic constraints for generating peptides with defined secondary structures. We have described how 1,1′-ferrocenedicarboxylic acid can be used to hold a peptide in a helical conformation [4] and how tungsten–alkyne coordination can be used to constrain peptide turn conformations [5]. Given our experience with tungsten–alkynylpeptide coordination [5–8] and the presence of an alkyne in **2** we set out to answer two questions. First, would the alkyne group in **2** coordinate to the tungsten? Although others have found that diphenylacetylene itself will coordinate to tungsten [6], **2** is a more highly substituted diphenylacetylene. It may not react in the same manner as diphenylacetylene. Second, if the alkyne does coordinate to the tungsten, will the peptide retain the β-sheet conformation? It has been shown that coordination of an alkyne to tungsten will bend the bond angles around the alkyne carbons [6]. This bending of the bond angles might disrupt the hydrogen bonding pattern observed in **2**, breaking up the β-sheet conformation.

This paper describes results that demonstrate that the alkyne of the substituted diphenylacetylene will coordinate to tungsten, and that the β-sheet conformation is maintained after coordination.

Results

Synthesis of the substituted diphenylacetylenes

In their 1995 paper Kemp and Li outlined the synthetic route to **1**, but did not provide exact experimental details. Those details are

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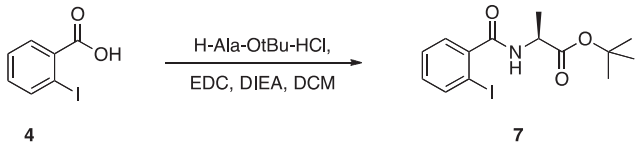
provided in the Ph.D. thesis of Li [9]. We report here our findings on how best to assemble the diphenylacetylene. The synthetic route employs both 2-ethynylaniline (**3**) and 2-iodobenzoic acid (**4**), which are commercially available, as the starting chemicals.

3 **4**

Acylation of the amine group in **3** is not easy to accomplish. For example, to attach a Boc protecting group to this amine requires a reflux in THF [7]. In our hands, this procedure produced a 62% yield of the urethane **5** (Scheme 1). To acylate the amine in **3** with an N-protected amino acid derivative, we examined a number of peptide coupling reagents; most coupling reagents (for example, carbodiimides) provided **6** in poor yield. The best yields were obtained using either the PyBOP reagent [8], or by preforming the symmetrical anhydride [9] and reacting it with **3** (Scheme 1).

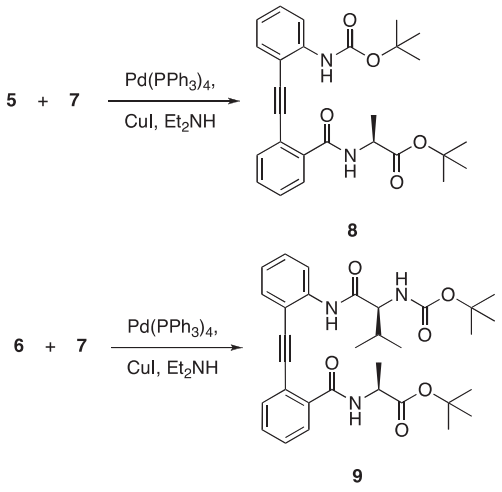
The carboxylic acid in **4** is readily acylated using peptide coupling reagents. For example treatment of **4** with alanine *t*-butyl ester and the water soluble carbodiimide EDC [10] provided pure **7** in moderate yield (Scheme 2).

With **5**, **6** and **7** in hand, assembly of the diphenylacetylene could be undertaken using the Sonogashira coupling [11]. Thus, **5** was reacted with **7** to yield, after purification by flash chromatography, **8** in 49% yield (Scheme 3). Likewise, **6** was reacted with **7** to yield, after purification by flash chromatography, **9** in 95% yield (Scheme 3). Both reactions used commercially available $Pd(PPh_3)_4$ as the catalyst, and diethylamine as the base.



4 **7**

Scheme 2.



8

9

Scheme 3.

*Coordination of **8** and **9** to tungsten*

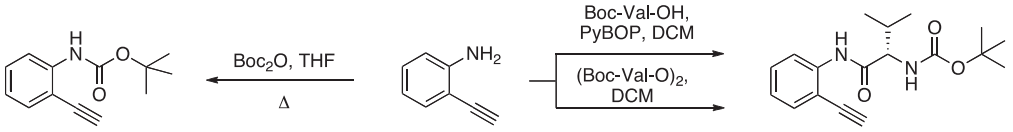
Reaction of 1 mol equivalent of **8** or **9** with 1 mol equivalent of $W(CO)_3(dmtc)_2$ [12] in degassed methylene chloride at room temperature and under an atmosphere of N_2 produced the monoalkyne complexes **10** and **11** (Scheme 4). These complexes have a deep green color, in contrast to $W(CO)_3(dmtc)_2$ which has an orange color. The change in color occurred very quickly, and the reactions were judged to be complete after 2 h. Once the reaction was complete the solvent was evaporated and the crude product purified immediately by flash chromatography. After purification complex **10**, as an inseparable mixture of the diastereomers **10a** and **10b**, was obtained in 55% yield. The generation of the two diastereomers was expected. They differ in the spatial arrangement of the two dmtc ligands relative to the alkyne, and are generated in the reaction that produces the monoalkyne complex. The formation of two diastereomers with tungsten–monoalkynylpeptide complexes was noted in a recent paper [13]. After purification, complex **11** was obtained in 58% yield as an inseparable (TLC and HPLC) mixture of the diastereomers **11a** and **11b**. The purity of **10** and **11** were assessed to be greater than 95% by HPLC. The yields for both reactions are not optimized. Both **10** and **11** are air sensitive, so they were stored under N_2. Like other recently studies of tungsten monoalkyne complexes [13], **10** and **11** produced an (M + Na − C) ion when analyzed by electrospray mass spectrometry in the presence of oxygen. Presumably, the monoalkyne complex loses a CO ligand but then reacts with molecular oxygen to yield the (M + Na − C) ion.

*Conformational analysis of **10** and **11***

With **10** and **11** in hand, we sought to determine their solution conformation; specifically, we sought to discover whether **10** and **11** adopt a β-sheet structure. Unfortunately we have been unable to generate crystals of **10** and **11** suitable for X-ray analysis. Consequently, NMR methods were used to probe their conformational behavior.

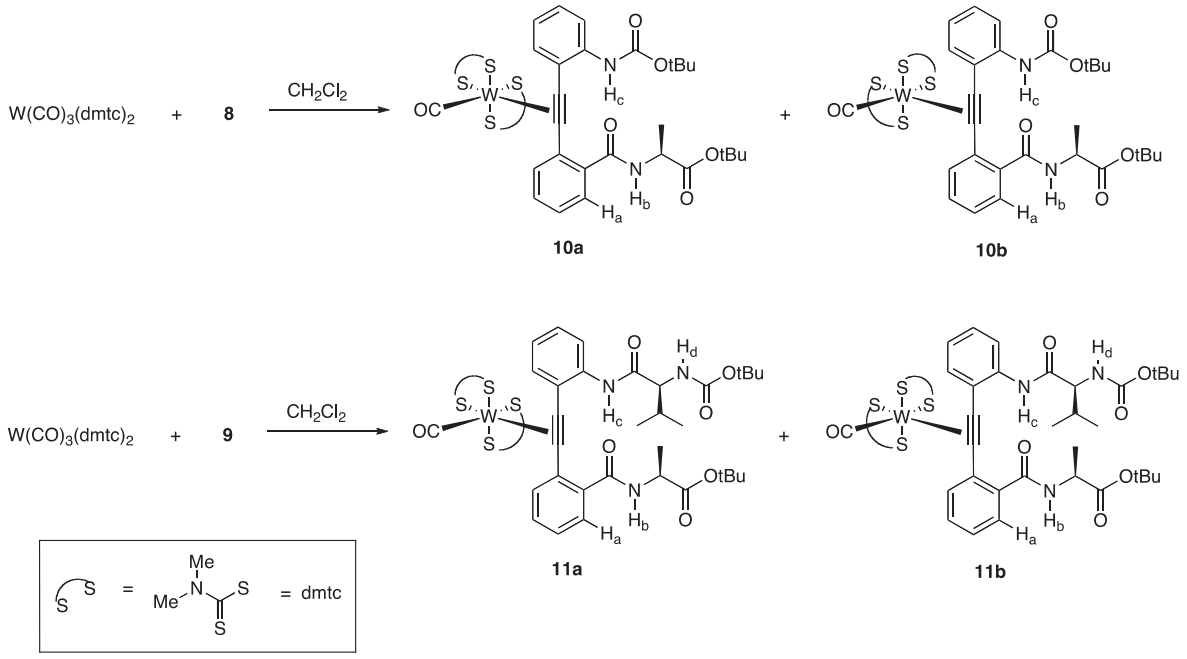
First, the ^1H NMR spectra of **10** and **11** were obtained in $CDCl_3$. Because **10** is a mixture of **10a** and **10b**, the spectra show two resonances for each proton. Some resonances closely overlap, while others show significant chemical shift differences. For example, in the spectrum of **10** the alanine $C_\alpha H$ proton appears as two multiplets at 4.1 and 4.2 ppm, with the two multiplets appearing in a nearly 1:1 ratio (Fig. 1). There are also two resonances for the aromatic and NH protons in **10**. The same is true for the spectrum of **11**, where the $C_\alpha H$, NH and aromatic protons all appear as two resonances in a nearly 1:1 ratio.

Second, to assign all the resonances in the ^1H NMR spectra, the COSY spectra for **10** and **11** were obtained. Aiding in the process of assignment were the resonance assignments for **8** and **9**, which



5 **3** **6**

Scheme 1.

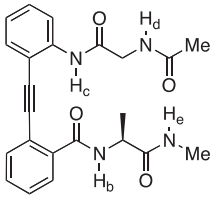


Scheme 4.

were also obtained from COSY spectra. Because each unique proton in **10** and **11** gives rise to two resonances, care was taken to identify both resonances.

Third, both **10** and **11** were examined in a DMSO titration [14–19]. In this experiment, the molecule under study is dissolved in a non-hydrogen bonding solvent (like $CDCl_3$) and the NMR spectrum recorded. Subsequently, small amounts of DMSO-d_6 are added to the NMR tube, and the spectrum in the solvent mixture is recorded. Because of the interactions with the DMSO-d_6, NH protons exposed to the solvent will experience a large change in chemical shift during the course of the DMSO titration; NH protons involved in intramolecular hydrogen bonds, however, do not interact with the DMSO and their chemical shifts vary very little during the DMSO titration.

Kemp and Li performed DMSO titrations on **12** and **13** [9]. In both of these species the chemical shifts of NH_c and NH_e were essentially invariant as the solvent was changed from $CDCl_3$ to DMSO-d_6, while the chemical shifts of NH_b and NH_d changed by approximately 1.7 ppm. This behavior was consistent with the conclusion that **12** and **13** adopt an anti-parallel β-sheet conformation.



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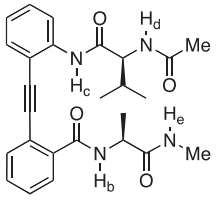

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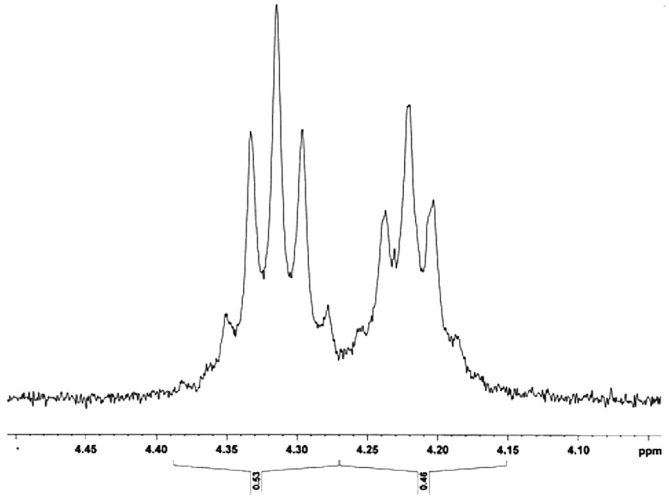


Fig. 1. A portion of the ^{1}H NMR spectrum of **10** showing the two resonances for the alanine $C_\alpha H$ proton. The two resonances arise because the synthesis of **10** generates two diastereomers, **10a** and **10b**.

Given in Figs. 2 and 3 are the results from the DMSO titrations of **10** and **11**. Since there are two resonances for each proton in **10** and **11**, the chemical shift changes for both resonances were tracked. The DMSO titration of **10** (Fig. 2) shows that the chemical shift of the NH_b proton undergoes a significant change as the DMSO-d_6 is added, indicating that NH_b is exposed to the solvent. On the other hand, the data shows that the chemical shift of the NH_c proton changes very little as the DMSO-d_6 is added, indicating that this NH is involved in an intramolecular hydrogen bond. NH_c can only be in an intramolecular hydrogen bond if **10** has maintained the β-sheet structure upon coordination of **8** to tungsten. These results match those reported by Kemp and Li [9].

Similarly, the DMSO titration of **11** (Fig. 3) shows that the chemical shifts of the NH_b and NH_d protons undergo a significant change as the DMSO-d_6 is added. In the case of NH_b, only the first few data points could be collected; after that point the NH_b proton was no longer visible as it overlapped with the aromatic resonances from the diphenylacetylene. However, the data collected shows a very sharp change in the chemical shift. The data for NH_b and NH_d protons in **11** indicates that they are

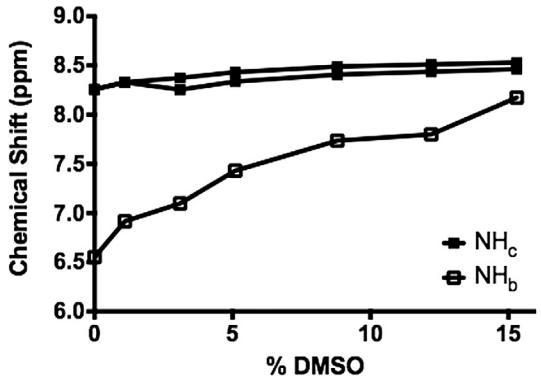


Fig. 2. DMSO titration results for the mixture of **10a** and **10b**. The two overlapping resonances for proton NH_b (see Scheme 4) start at 6.5 ppm and rises to 8.3 ppm over the course of the experiment, while the two resonances for the proton NH_c (see Scheme 4) start at 8.3 ppm and rise to only 8.5 ppm. The data shows that NH_b is not involved in an intramolecular hydrogen bond, while the NH_c is part of an intramolecular hydrogen bond.

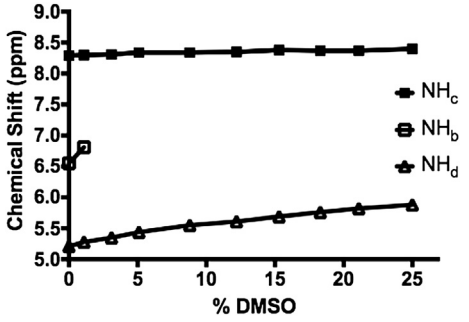


Fig. 3. DMSO titration results for the mixture of **11a** and **11b**. The two overlapping resonances for NH_d (see Scheme 4) start at 5.2 ppm and rises to 5.9 ppm over the course of the experiment, while the two resonances for NH_c (see Scheme 4) start at 8.3 ppm and rise to only 8.5 ppm. The two resonances for NH_b start at 6.5 ppm and rise quickly to 7.0 ppm before they are lost from view underneath the resonances from the diphenylacetylene protons. The data shows that the alanine NH_d and NH_b are not involved in an intramolecular hydrogen bond, while the NH_c is part of an intramolecular hydrogen bond.

exposed to the solvent. In contrast, the chemical shift of NH_c in **11** does not change significantly as the DMSO-d_6 is added. This indicates that this proton is involved in an intramolecular hydrogen bond. That the NH_c is involved in an intramolecular hydrogen bond shows that the β-sheet structure is maintained when **9** is coordinated to tungsten. These results also match those reported by Kemp and Li [9].

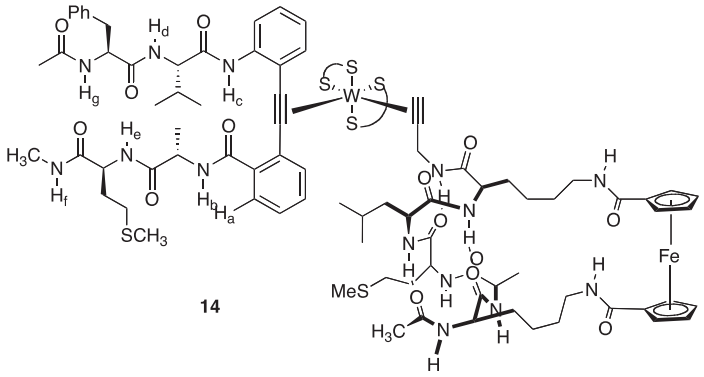
In addition to the DMSO titration data, the NOESY spectra for **10** and **11** in $CDCl_3$ were also obtained. As noted by Kemp and Li in their work, a signature NOE found in these β-sheet diphenylacetylenes is between the aromatic hydrogen ortho to the carboxyl group (H_a in Scheme 4), and the NH proton adjacent to that carboxyl group (NH_b in Scheme 4). The NOESY spectra of **10** and **11** both show a strong crosspeak between H_a and NH_b. This too confirms that the peptide portions of **10** and **11** adopt a β-sheet conformation.

Discussion

Taken together, the DMSO titration and NOESY data show that coordination of tungsten to **8** and **9** does not disrupt the β-sheet structure. Both monoalkyne complexes **10** and **11** adopt solution conformations where the two phenyl rings align to promote intramolecular hydrogen bonding. This work demonstrates that the tungsten–alkyne coordination can be used to generate organometallic β-sheet peptides.

There are several reports in the literature concerning the use of metal ions or organometallic entities for nucleation of β-sheets. In 1995 Schneider and Kelly linked two peptides to a bipyridine, and then used coordination of Cu^{+2} to hold the two peptides in an anti-parallel β-sheet conformation [20]. In 2005 König and co-workers prepared two peptides bearing ligands similar to EDTA at the N- and C-termini of two peptides; coordination of Zn^{+2} to these ligands caused the two peptides to adopt an anti-parallel β-sheet conformation [21]. In 2008 Breit and co-workers prepared peptides bearing phosphine ligands at their N- and C-termini; upon coordination of the phosphines to Pt^{+2} the two peptides adopted an anti-parallel β-sheet conformation [22]. Because the spacing of the Cp rings in ferrocene is close to the distance between the two peptides in a β-sheet, a number of β-sheets involving 1,1′-disubstituted ferrocenes have been reported by Hirao [23], Metzler-Nolte [24,25] and Kraatz [26,27]. In all of these efforts, the metal or the organometallic was used to form and maintain the sheet structure. A novel aspect of the work described here is that a preformed sheet is coordinated to a metal (tungsten) via an organometallic linkage, and the preformed sheet retains its structure.

Both **10** and **11** are monoalkyne complexes and have a CO ligand that is labile. This CO could be replaced by other ligands, for example another alkyne to generate a tungsten bis-alkyne complex. In other work from this laboratory, we have explored the nature of these bis-alkyne complexes [6]. A potential application for complexes like **10** and **11** would be the formation of novel *de novo* proteins having defined secondary and tertiary structure. For example, a species like **10** or **11** could be reacted with a helical peptide [4] bearing an alkyne to generate a tungsten bis-alkyne complex (**14**) that would link together helix and sheet domains.



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Experimental section

General procedures

2-Ethynylaniline, anisole, and sodium dimethyldithiocarbamate hydrate were purchased from Aldrich Chemical. Copper (I) iodide, 2-iodobenzoic acid, 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU), dimethylformamide (DMF), trifluoroacetic acid (TFA), diethylamine (Et_2NH), tetrahydrofuran (THF), acetic anhydride, di-tert-butyl dicarbonate (Boc_2O), 1-ethyl-3-[3-dimethylaminopropyl]carbodiimide hydrochloride (EDC), tetraethylammonium iodide, and chlorobenzene were purchased from Acros Organics. Diisopropylethylamine (DIEA), methanol, ethanol, hexanes, ethyl acetate, methylene chloride, toluene, ethyl ether, hydrochloric acid, sodium hydroxide, magnesium sulfate, and iodine were purchased from Fisher Scientific. Chloroform-*d* ($CDCl_3$), dimethylsulfoxide-d_6 (DMSO-d_6), acetone-d_6, and methylene chloride-d_2 (CD_2Cl_2) were purchased from Cambridge Isotope Laboratories, Inc. Tetrakis(-triphenylphosphine)palladium(0) and tungsten carbonyl were purchased from Strem Chemicals. Amino acid derivatives, PyBOP, and piperidine were purchased from Chem Impex International. Silica gel for flash chromatography was purchased from Silicycle. NMR spectra were obtained on a Bruker Avance III 400 MHz instrument. Electrospray mass spectra were obtained on an LCQ APCI/Electrospray LC MS–MS. Samples for mass spectral analysis were dissolved in MeOH (approximately 1 mg/mL) in borosilicate glass test tubes. Theoretical mass spectral isotope patterns were calculated using the Sheffield Chemputer [28]. HPLC analyses were performed on an Hitachi Elite LaChrom HPLC system equipped with L-2450 diode array detector, an L-2200 autosampler and an L-2130 pump. A Phenomenex Luna 5 μm Silica (2) 100 Å LC Column (250 × 4.6 mm) was used as the stationary phase. The mobile phase involved a linear gradient program using two solvents, 0.1% trifluoroacetic acid and acetonitrile. The gradient program started at 100% trifluoroacetic acid and changed to 20% trifluoroacetic acid/80% acetonitrile over the course of 12 min. The solvent was then held at 20% trifluoroacetic acid/80% acetonitrile for an additional 2 min.

Preparation of **5** [7]

0.343 mL of 2-ethynylaniline (**3**, 3.0 mmol, 1.0 equiv) and 0.658 g of di-tert-butyl dicarbonate (3.0 mmol, 1.0 equiv) were dissolved in 3 mL THF, and the resulting solution brought to reflux. After 7 h the solvent was evaporated leaving a crude, brown oil. This oil was purified by flash chromatography (21:1 hexanes:ethyl acetate) to yield 0.402 g (62%) of **5** as an oil: TLC, R_f 0.16 (20:1 hexanes:ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 8.19 (1H, d, J = 8.5 Hz), 7.45 (1H, d, J = 7.6 Hz), 7.40 (1H, s), 7.36 (1H, t, J = 7.9 Hz), 7.00 (1H, t, J = 7.6 Hz), 3.50 (1H, s), 1.55 (9H, s). ESMS, M + Na ion theoretical isotope pattern calculated for $C_{13}H_{15}NO_2Na$ [28]: 240 (100%), 241 (14.7%), 242 (1.4%); Found: 240 (100%), 241 (24.5%), 242 (2.2%).

Preparation of **6**

To a solution of 0.330 mL DIEA (2.0 mmol, 2.0 equiv) and 0.519 g PyBOP (1.0 mmol, 1.0 equiv) in 3 mL CH_2Cl_2 was added 0.218 g Boc-Val-OH (1.0 mmol, 1.0 equiv) and 0.125 mL of **3** (1.1 mmol, 1.1 equiv). The solution was stirred at 23 °C for 12 h. After the solvents were evaporated the remaining residue was redissolved in 25 mL ethyl acetate and washed with 3 × 25 mL of 1 M HCl, 2 × 25 mL of saturated $NaHCO_3$, and 2 × 25 mL of brine. The ethyl acetate was dried ($MgSO_4$), filtered and evaporated. Flash chromatography (20:1 hexanes:ethyl acetate for 20 fractions, followed by 10:1 hexanes:ethyl acetate) provided 0.084 g (28%) of pure **6**: TLC, R_f 0.16 (4:1 hexanes:ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 8.53 (1H, s), 8.44 (1H, d, J = 8.3 Hz), 7.48 (1H, d, J = 7.7 Hz), 7.39 (1H, t, J = 7.9 Hz), 7.09 (1H, t, J = 7.6 Hz), 5.12 (1H, d, J = 6.4 Hz), 4.18 (1H, m), 3.51 (1H, d, J = 2.8 Hz), 2.35 (1H, m), 1.47 (9H, s), 1.05 (3H, d, J = 6.9 Hz), 0.99 (3H, d, J = 6.9 Hz). ESMS, M + Na ion theoretical isotope pattern calculated for $C_{18}H_{24}N_2O_3Na$ [28]: 339 (100%), 340 (20.6%), 341 (2.6%); Found: 339 (100%), 340 (25.7%), 489 (4.2%).

Preparation of **7**

To a suspension of 0.500 g (2.02 mmol, 1.0 equiv) of 2-iodobenzoic acid in 2 mL CH_2Cl_2 was added a solution of 0.844 g (2.22 mmol, 1.1 equiv) of HATU dissolved in 1 mL CH_2Cl_2 and 1 mL DMF. The resulting clear solution stirred at 23 °C for 5 min, after which 367 mg (2.02 mmol, 1.0 equiv) of alanine *t*-butyl ester hydrochloride, 1 mL CH_2Cl_2, and 2.0 mL (11.5 mmol, 5.5 equiv) of DIEA were added. The resulting clear, light yellow solution stirred for 48 h at 23 °C. The reaction mixture was poured into 50 mL EtOAc and washed 3 × 25 mL 1 M HCl, 3 × 20 mL 1 M NaOH, and 1 × 25 mL brine. The organic layer was dried ($MgSO_4$), filtered and evaporated to yield 798 mg of crude product as a light yellow oil. Following purification by flash chromatography (4:1 hexanes:EtOAc) 687 mg of pure **7** was obtained as a clear colorless oil: TLC, R_f 0.29 (4:1 hexanes:ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.87 (1H, dd, J = 8.1, 1.0 Hz), 7.43 (1H, dd, J = 7.6, 1.8 Hz), 7.38 (1H, dt, J = 7.5, 1.1 Hz), 7.10 (1H, dt, J = 7.6, 1.8 Hz), 6.41 (1H, d, J = 6.8 Hz), 4.67 (1H, pentet, J = 7.2 Hz), 1.53 (3H, d, J = 7.1 Hz), 1.50 (9H, s). ESMS, M + Na ion theoretical isotope pattern calculated for $C_{14}H_{18}NO_3Na$ [28]: 398 (100%), 399 (15.8%), 400 (1.8%); Found: 240 (100%), 241 (14.6%), 489 (1.5%).

Preparation of **8**

To a solution under N_2 of 0.043 g of **5** (0.20 mmol, 1.0 equiv) and 0.075 g of **7** (0.20 mmol, 1.0 equiv) in 3 mL degassed diethylamine was added 0.012 g CuI (0.063 mmol, 0.30 equiv) and 0.024 g $Pd(PPh_3)_4$ (0.021 mmol, 0.10 equiv). The solution was stirred at 23 °C under N_2 for 48 h. After evaporation of the solvent the remaining residue was redissolved in 25 mL ethyl acetate and washed 3 × 25 mL of 1 M HCl, 2 × 25 mL of 1 M NaOH, and 2 × 25 mL brine. The ethyl acetate was dried ($MgSO_4$), filtered and evaporated. Flash chromatography (20:1 hexanes:ethyl acetate) provided 0.045 g (49%) of pure **8** as a light tan solid: TLC, R_f 0.14 (4:1 hexanes:ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 (1H, d, J = 8.4 Hz), 7.83 (1H, d, J = 7.4 Hz), 7.75 (1H, s), 7.64 (1H, d, J = 7.4 Hz), 7.52–7.42 (3H, m), 7.33 (1H, t, J = 8.0 Hz), 7.24 (1H, d, J = 7.2 Hz), 6.90 (1H, t, J = 7.6 Hz), 4.77 (1H, pentet, J = 7.21 Hz), 1.58 (9H, s), 1.49 (3H, d, J = 4.8 Hz), 1.45 (9H, s). ESMS, M + Na ion theoretical isotope pattern calculated for $C_{27}H_{32}N_2O_5Na$ [28]: 487 (100%), 488 (30.5%), 489 (5.5%); Found: 487 (100%), 488 (41.5%), 489 (16.3%).

Preparation of **9**

To a solution under N_2 of 0.031 g of **6** (0.098 mmol, 1.0 equiv) and 0.037 g of **7** (0.099 mmol, 1.0 equiv) in 4 mL degassed diethylamine was added 0.010 g CuI (0.052 mmol, 0.5 equiv) and 0.014 g $Pd(PPh_3)_4$ (0.012 mmol, 0.12 equiv). The solution was stirred at 23 °C under N_2 for 48 h. The solvents were evaporated and the crude product purified by flash chromatography (9:1 hexanes:ethyl acetate for the initial 300 mL of eluant, 4:1 hexanes:ethyl acetate for the next 100 mL of eluant). Pure **9** (52 mg, 95%) was obtained as a clear oil in the fractions that eluted with 4:1 hexanes:ethyl acetate: TLC, R_f 0.35 (4:1 hexanes/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.26 (1H, s), 8.55 (1H, d, J = 8.6 Hz), 7.69 (1H, d, J = 7.8 Hz),

7.53–7.31 (5H, m), 7.07 (1H, t, $J = 7.6$ Hz), 6.90 (1H, d, $J = 7.1$ Hz), 5.90 (1H, d, $J = 9.1$ Hz), 4.81 (1H, m), 4.75 (1H, m), 2.33 (1H, m), 1.51 (3H, d, $J = 7.0$ Hz), 1.41 (9H, s), 1.34 (9H, s), 1.04 (3H, d, $J = 6.8$ Hz), 0.99 (3H, d, $J = 6.8$ Hz); ESMS, M + Na ion theoretical isotope pattern calculated for $C_{32}H_{41}N_3O_6Na$ [28]: 586 (100%), 587 (36.4%), 588 (7.7%); Found: 586 (100%), 587 (30.6%), 588 (5.9%).

*Preparation of **10***

To a solution of 0.060 g (0.12 mmol, 1.0 equiv) of $W(CO)_3(dmtc)_2$ in 6 mL of degassed CH_{2Cl2} under N_2 was added a solution of 0.055 g (0.12 mmol, 1.0 equiv) of **8** dissolved in 7 mL CH_2Cl_2. The solution was stirred under N_2 for 3 h; during this time the solution turned color from orange to dark green. The solvent was evaporated, leaving 0.105 g of crude product. Flash chromatography (12:1 hexanes:EtOAc followed by 8:1 hexanes:EtOAc) yielded 0.060 g (55%) of **10** as a green solid: TLC, R_f 0.48 (8:1 hexanes:ethyl acetate); HPLC, R_t 12.4 min; ^{1}H NMR (400 MHz, CD_2Cl_2): δ 8.12, 8.05 (1H, 2 br s), 8.06, 8.04 (1H, 2d, $J = 6.0$ Hz), 7.70 (1H, 2d, $J = 7.8$ Hz), 7.67 (1H, 2d, $J = 7.8$ Hz), 7.51, 7.50 (1H, 2dt, $J = 7.6$ Hz, 1.3 Hz), 7.34 (1H, 2tt, $J = 7.6$ Hz, 1.2 Hz), 7.28 (1H, 2tt, $J = 7.7$ Hz, 1.6 Hz), 7.15, 7.13 (1H, 2dt, $J = 7.0$ Hz, 1.2 Hz), 7.00, 6.89 (1H, 2d, $J = 7.5$ Hz), 6.58 (1H, m), 4.20, 4.10 (1H, 2 pentets, $J = 7.3$ Hz, 6.8 Hz), 3.31–3.23 (12H, 6s), 1.49, 1.45 (9H, 2s), 1.31 (3H, m), 1.31, 1.29 (9H, 2s); ESMS M + Na − C theoretical isotope pattern [28]: 925 (60.5%), 926 (57.5%), 927 (100%), 928 (43.1%), 929 (89.0%), 930 (34.4%), 931 (20.5%), 932 (6.4%); Found: 925 (62.1%), 926 (57.9%), 927 (100%), 928 (44.3%), 929 (94.8%), 930 (35.0%), 931 (20.6%), 932 (77%).

*Preparation of **11***

To a solution under N_2 of 0.026 g of **9** (0.046 mmol, 1.05 equiv) in 4 mL of degassed CH_2Cl_2 was added 0.022 g of $W(CO)_3(dmtc)_2$ (0.044 mmol, 1.0 equiv). The resulting solution was stirred under N_2 for 24 h at 23 °C. Over this time the color changed from orange to dark green. The solvent was evaporated, leaving a crude green solid. Flash chromatography (3:1 hexanes:ethyl acetate followed by 2:1 hexanes:ethyl acetate followed by 1:1 hexanes:ethyl acetate) was used to obtain 26 mg (58%) of pure **11**: TLC, R_f 0.40 (1:1 hexanes:ethyl acetate); HPLC, R_t 12.6 min; ^{1}H NMR ($CDCl_3$) δ 8.40 (1H, d, $J = 8.6$ Hz), 8.33 (1H, br s), 8.27 (1H, d, $J = 8.2$ Hz), 7.71 (1H, d, $J = 7.6$ Hz), 7.62 (1H, d, $J = 7.7$ Hz), 7.49 (1H, dt, $J = 7.6$ Hz, 1.2 Hz), 7.45 (1H, dt, $J = 7.4$ Hz, 1.0 Hz), 7.32–7.15 (3H, m), 7.07 (1H, m), 6.82, 6.57 (2 d, $J = 7.4$ Hz, 6.5 Hz), 5.30, 5.22 (1H, 2 d, $J = 9.0$ Hz, 8.5 Hz), 4.34, 4.30 (1H, 2 m), 4.13, 3.66 (1H, 2 m), 7.30–7.20 (12H, m), 1.96, 1.79 (1H, m), 1.49 (9H, s), 1.43, 1.42 (9H, 2s), 1.30 (3H, d, $J = 6.8$ Hz), 0.83 (3H, d, $J = 6.8$ Hz), 0.75 (3H, d, $J = 6.8$ Hz). ESMS M + Na − C theoretical isotope pattern [28]: 1024 (58.4%), 1025 (58.9%), 1026 (100%), 1027 (47.5%), 1028 (88.7%), 1029 (38.5%), 1030 (22.0%), 1031 (7.5%); Found: 1024 (62.9%), 1025 (57.0%), 1026 (100%), 1027 (50.6%), 1028 (89.3%), 1029 (32.9%), 1030 (19.2%), 1031 (6.8%).

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jorganchem.2014.08.004.

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