Available online at www.sciencedirect.com
SCIENCE DIRECT®
Journal of Organometallic Chemistry 689 (2004) 4837–4847
Journal of Organometallic Chemistry
www.elsevier.com/locate/jorganchem

N-terminus to C-terminus metallacyclicpeptides employing tungsten–alkyne coordination

Timothy P. Curran *, Richard S.H. Yoon, Brian R. Volk

Department of Chemistry, Trinity College, 300 Summit Street, Hartford, CT 06106-3100, USA

Received 29 July 2004; accepted 27 September 2004
Available online 5 November 2004

Abstract

The capacity of using tungsten–alkyne coordination to form metallacyclicpeptides was examined. Dialkynyl species **1**, **2** and **3** were prepared. **1** is a dialkyne derivative of ammonia, **2** is a dialkyne derivative of alanine, while **3** is a dialkyne derivative of the dipeptide alanylalanine. In **2** and **3** the two alkyne groups were appended at the N- and C-termini. The N-terminal alkyne was prepared by acylating the N-terminal amine with propargylchloroformate. The C-terminal alkyne was introduced by acylating the C-terminal carboxylic acid with propargylamine. Outcomes of metallacyclization reactions were assessed using ^{1}H NMR spectroscopy and electrospray positive ion mass spectrometry. Both **2** and **3** underwent successful cyclization to yield the metallacyclicpeptides **16** and **17**, respectively. However, **1** did not cyclize; instead, it formed a variety of acyclic and cyclic oligomeric tungsten–bis(alkyne) species. The failure of **1** to cyclize is attributed to its inability to position its two alkyne groups parallel to each other and spaced 6.5 Å apart. The ^{1}H NMR spectra for **16** and **17** show that these metallacyclicpeptides exist as a complex mixture of isomers that differ in how the ligands are positioned around the tungsten center. At elevated temperatures metallcyclicpeptide **17** will rapidly interconvert between the various isomers. In contrast, **16** does not readily interconvert between isomers, even at elevated temperatures. That **16** does not rapidly interconvert between isomers, even at 90 °C, is attributed to the tight packing and limited conformational freedom of this metallacyclicpeptide.

Keywords: Tungsten; Alkynes; Metallacyclicpeptide; Conformation

1. Introduction

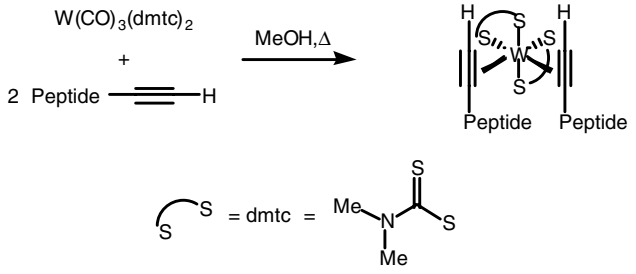
Uncovering methods for coordination of amino acids and peptides to transition metals is a growing research area in bioorganometallic chemistry [1]. As part of this effort, we have been exploring the use of alkyne ligands [2] for coordinating tungsten to amino acids and peptides [3]. In this approach, the alkyne is introduced onto the amino acid or peptide, and two of the resulting alkynylamino acids or alkynylpeptides are then coordinated to tungsten (Scheme 1).

Another possible use of the tungsten–alkyne coordination chemistry with peptides is the formation of metallacyclicpeptides. In this approach, a peptide bearing two alkyne groups is joined to the tungsten to form a macrocyclic ring (Scheme 2).

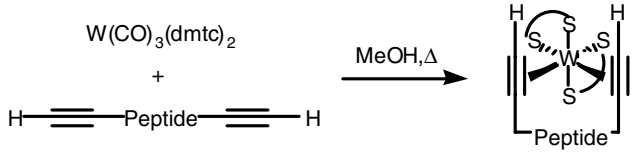
In order to determine whether this second approach would work, the dialkynyl compounds **1**–**3** (Scheme 3) were prepared and reacted with $W(CO)_3(dmtc)_2$. The common element in **1**–**3** is the presence of a terminal alkyne group at both ends of the molecule. With **2** and **3**, the alkyne group appears at the N- and C-termini of the peptide chain. We report here that **1** does not form the desired complex; instead it forms three other bis(alkyne) complexes. However, both **2** and **3** do form

* Corresponding author. Tel.: +1 8602975276; fax: +1 8602975129.
E-mail address: timothy.curran@trincoll.edu (T.P. Curran).

0022-328X/$ - see front matter © 2004 Elsevier B.V. All rights reserved.
doi:10.1016/j.jorganchem.2004.09.062



Scheme 1.



Scheme 2.

the desired metallacyclicpeptides, and the conformational behavior of these complexes is examined.

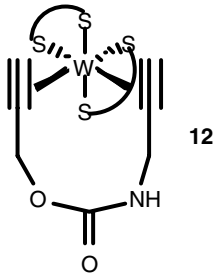
2. Results and discussion

2.1. Synthesis of 1–3

The syntheses of **1**–**3** are shown in Scheme 4A–C. Treatment of propargylchloroformate (**4**) with propargylamine hydrochloride (**5**) in the presence of a trialkylamine base cleanly yields **1** (Scheme 4A). To prepare **2** (Scheme 4B), Boc–Ala–OSu (**6**) was reacted with propargylamine hydrochloride (**5**) in the presence of a trialkylamine base to produce **7** [3]. Subsequent treatment of **7** with trifluoroacetic acid (which removes the Boc protecting group) yields the salt **8**. Without further purification, **8** is reacted with propargylchloroformate (**4**) in the presence of a trialkylamine base to produce **2** (Scheme 4B). The preparation of **3** (Scheme 4C) began with the acylation of Boc–Ala–Ala–OH (**9**) with propargylamine hydrochloride (**5**) using a carbodiimide coupling reagent (EDC) to yield **10**. Subsequent treatment of **10** with trifluoroacetic acid (which removes the Boc protecting group) yielded the salt **11**, which was then reacted with propargylchloroformate (**4**) in the presence of a trialkylamine base to produce **3**.

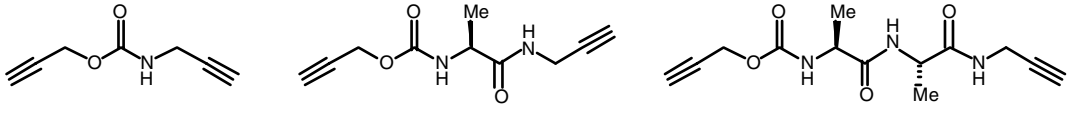
2.2. Reaction of 1 with W(CO)3(dmtc)2

Compound **1** was reacted with $W(CO)_3(dmtc)_2$ in an effort to form the desired metallacyclic product, **12**. In order to minimize the chance for oligomer formation, **1** was reacted with $W(CO)_3(dmtc)_2$ under high dilution (1 mM) conditions. Thus, **1** was dissolved in MeOH at a concentration of 1 mM, the solution brought to reflux, and a solution of $W(CO)_3(dmtc)_2$ dissolved in CH_2Cl_2 was added slowly to the MeOH solution of **1**. Addition of $W(CO)_3(dmtc)_2$ to the colorless solution of **1** initially produced a light green solution. The green color indicated formation of a monoalkyne complex, which presumably has the formula $W(\mathbf{1})(CO)(dmtc)_2$ [4]. This green color slowly changed to a yellow color during the next 2 h of reflux. The yellow color indicated formation of a tungsten–bis(alkyne) complex [5]. Evaporation of the solvents produced a crude, yellow solid. Analysis of the solid by TLC showed three major spots that possessed a yellow color. Flash chromatography was used to isolate the three compounds that give rise to these spots.

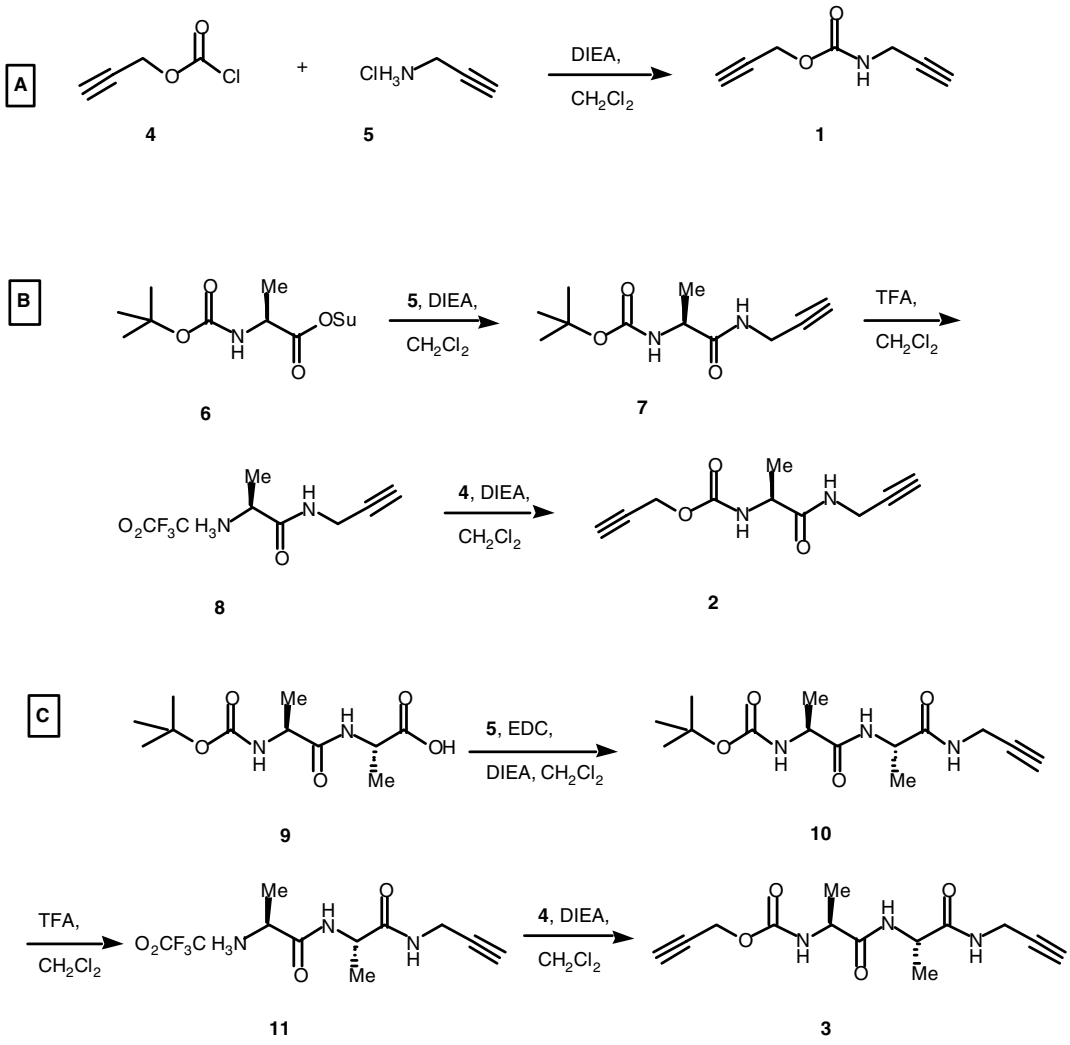


The three yellow products isolated from the reaction were analyzed by positive ion ESMS [6]. Because tungsten possesses four major, naturally occurring isotopes, the molecular ions for tungsten–bis(alkyne) complexes generate unique and characteristic peak patterns [3]. Analysis of all three products showed that none were the desired metallacyclic product, **12**. The ESMS data, however, could be used to ascertain the identities of the three yellow products.

The product obtained in the highest, purified yield (15%) gave an M + Na ion with peaks centered around 721 *m*/*z*. This M + Na ion is consistent with a structure having one tungsten, two dmtc groups, and two molecules of **1** [$W(\mathbf{1})_2(dmtc)_2$ = **13**]. This bis(alkynylpeptide) complex formed even with the concentrations of the



Scheme 3.



Scheme 4.

reactants being very low. One of the possible structures for **13** is shown in Scheme 5.

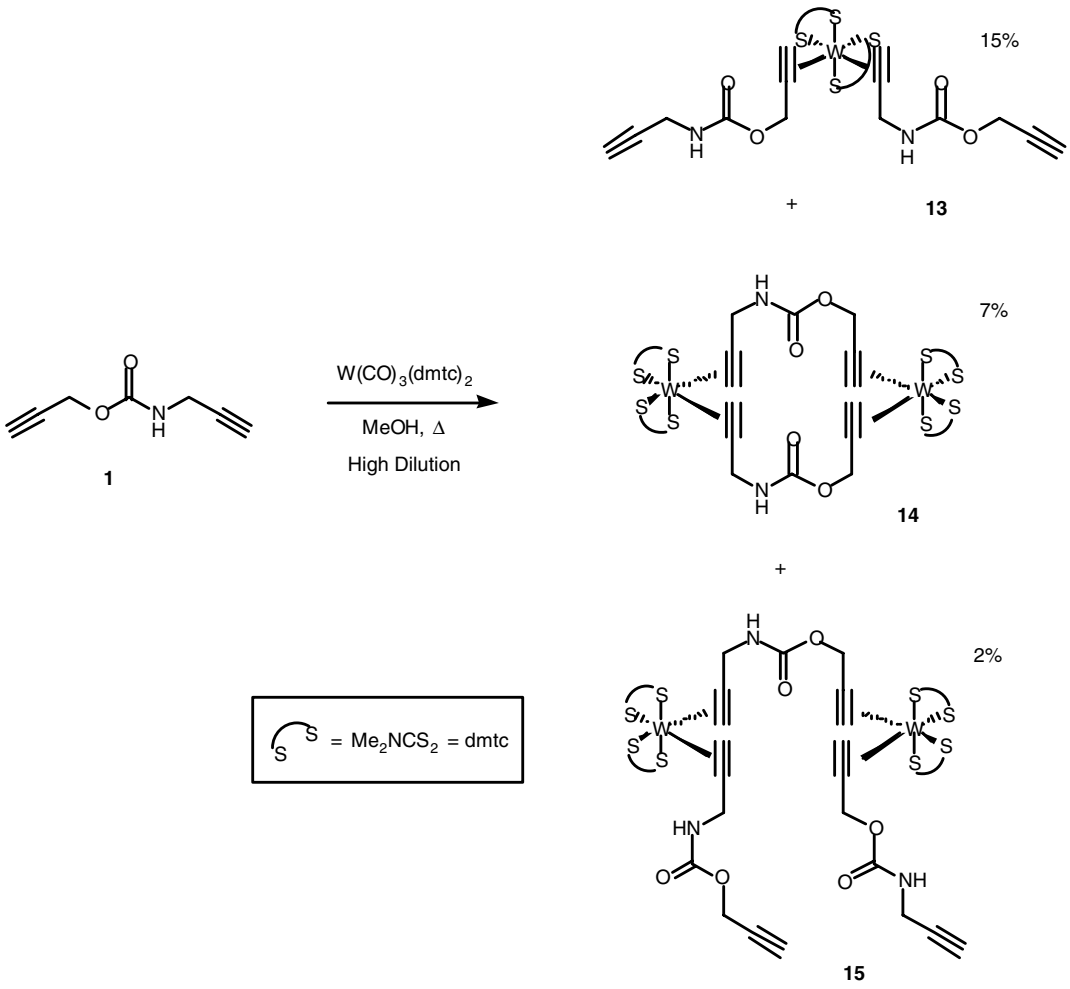
The second product isolated and purified from this reaction (7%) produced molecular ion peaks in the ESMS centered around 1145 *m/z*. This M + Na ion is consistent with a structure having two tungstens, four dmtc groups and two molecules of **1**, $[W_2(\mathbf{1})_2(dmtc)_4 = \mathbf{14}]$. This molecule has to possess a metallacyclic structure, with the tungstens bridged by two molecules of **1**; one of the possible structures for **14** is shown in Scheme 5.

The third product isolated and purified (2%) from the reaction of **1** with $W(CO)_3(dmtc)_2$ gave M + Na peaks in the ESMS centered around 1282 *m/z*. This M + Na ion is consistent with a structure having two tungstens, four dmtc groups and three molecules of **1** $[W_2(\mathbf{1})_3(dmtc)_4 = \mathbf{15}]$. This species is a cross between **13** and **14**. A possible structure for **15** is shown in Scheme 5.

The absence of the desired product from this reaction mixture, and the observed formation of **13**, **14**, and **15**, indicates that the metallacyclization of **1** with tungsten here is not possible. Using data from X-ray crystal structures of tungsten bis(alkyne) complexes [2], it can be estimated that the two alkynes in these bis(alkyne) complexes need to be positioned parallel to each other and approximately 6.5 Å apart. A Dreiding model of **1** was constructed and examined. At their closest possible approach, the two alkynes in the model were approximately 7.2 Å apart. Thus it appears that **1** cannot position its two alkyne groups in close enough proximity to effect cyclization. From the Dreiding model of **1**, it is clear that the structural rigidity imposed on **1** by the urethane group keeps the two alkynes from being able to get within 6.5 Å of each other.

2.3. Cyclization of **2** with $W(CO)_3(dmtc)_2$

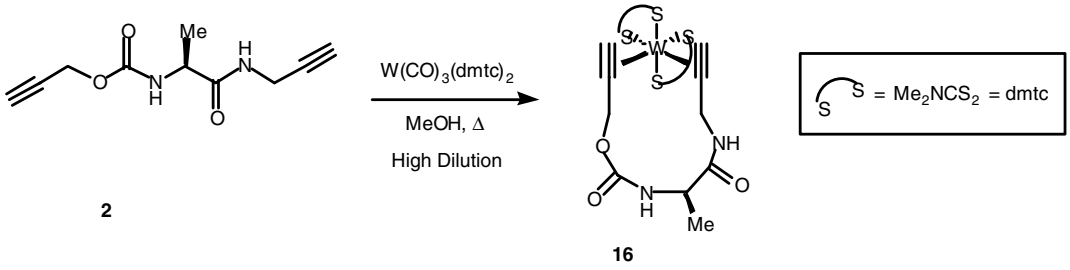
Compound **2**, the dialkynylalanine, was reacted with $W(CO)_3(dmtc)_2$ under high dilution conditions in an effort to form the desired metallacyclization product,



Scheme 5.

16 (Scheme 6). As with the reaction of **1**, addition of the $W(CO)_3(dmtc)_2$ to a refluxing, 1 mM solution of **2** in MeOH initially generated a light green solution, which on further heating turned yellow. Workup of the reaction and analysis by TLC showed the formation of one major yellow band. This compound was isolated and purified by flash chromatography. Analysis of the amorphous, yellow solid showed it to be the desired metallacyclicpeptide, **16**. The ESMS produced a series of peaks centered around 655 *m*/*z*, which match the peaks expected for the M + Na ion for **16**. The ^{1}H NMR spectrum also possessed all the resonances for the hydrogens expected in **16**, including the alkyne hydrogens at 11 ppm and the *N*-methyl hydrogens from the dithiocarbamates located in the 3.0–3.5 ppm region.

Because there are two different stereochemistries open to the dithiocarbamate ligands, and because there are two orientations open to each alkyne ligand, **16** appears as a mixture of these isomers. The isomerism open to 16 arises from what von Zelewsky refers to as "fuzzy



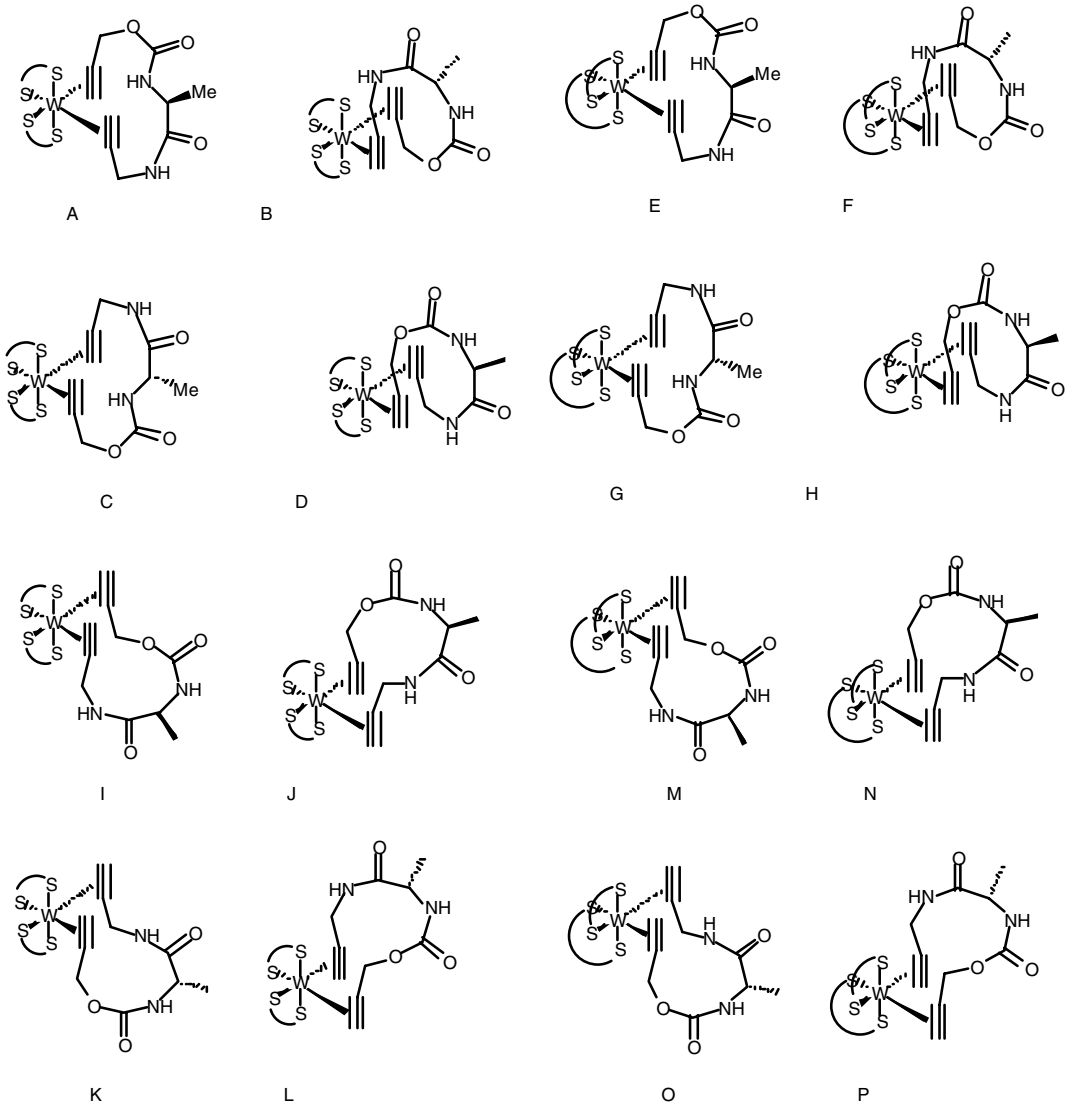
Scheme 6.

stereochemistry'' [7]. Shown in Scheme 7 are the various isomers open to **16**. First, there are two possible orientations for the two alkyne groups in **16**; they can be either anti to each other (indicated by those isomers that have their alkyne C–H bonds pointing in opposite directions, A–H) or they can be anti to each other (indicated by those isomers that have their alkyne C–H bonds pointing in the same direction, I–P). The *syn*- and *anti*-isomer groupings can be further divided into two groups defined by the two possible stereochemistries of the dithiocarbamate ligands around the tungsten; isomers A–D and I–L have one of the stereochemisties, while isomers E–H and M–P have the other. Finally, these last groupings of isomers can be further divided into two more groups that differ in the orientation of the peptide chain (N-terminus to C-terminus) relative to the tungsten; A–B, E–F, I–J, M–N have one of the orientations, while C–D, G–H, K–L, O–P have the other orientation.

Although it appears that there are 16 different isomers possible for **16**, in actuality there are eight possible isomers. This is true because each isomer shown in Scheme 7 has an identical twin. Thus, A is the same as C, and B is the same as D. Likewise, E and G are the same, as are F and H. Other identical pairs are I and L, J and K, M and P, and N and O. Because of these identical pairs, the actual number of possible isomers for **16** is 8 rather than 16.

If interconversion between these isomers is slow, then the ^{1}H NMR spectrum will show resonances from each isomer. Thus, the appearance of multiple peaks for a given hydrogen type in **16** indicates the presence of multiple isomers that either slowly interconvert or do not interconvert at all.

One set of hydrogens that can reveal the conformational behavior of **16** are the alkyne hydrogens that appear around 11 ppm. If **16** adopts only one of the



Scheme 7.

orientations shown in Scheme 7, then the ^{1}H NMR spectrum should show two singlets of equal intensity, one for each alkyne hydrogen. If **16** adopts two of the orientations, then the ^{1}H NMR spectrum should show four singlets, with pairs of the singlets having equal intensities. Likewise, if **16** adopts three of the orientations then there should be six singlets with three pairs of singlets having equal intensities. For every orientation adopted by **16**, another two signals for the alkyne hydrogens should be seen.

A similar type of analysis can be applied to the *N*-methyl hydrogens that appear between 3.0 and 3.5 ppm. If **16** adopts only one of the orientations in Scheme 7, then the ^{1}H NMR spectrum should show four *N*-methyl singlets. If **16** adopts only two of the orientations in Scheme 7, then the ^{1}H NMR spectrum should show eight *N*-methyl singlets. Likewise, if three of the orientations are adopted, then 12 *N*-methyl singlets will be visible in the ^{1}H NMR spectrum. For every orientation adopted by **16**, another four *N*-methyl singlets should be seen.

A quick inspection of the ^{1}H NMR spectrum of **16** shows that this molecule exists as more than one of the isomeric structures shown in Scheme 7, as there are multiple signals for all the hydrogen types present. Fig. 1(a) shows the alkyne hydrogen region (10.7–11.7 ppm), and Fig. 1(b) shows the *N*-methyl region (2.8–3.8 ppm) for **16**. The alkyne hydrogen region shows four distinct singlets, each possessing different intensities. The spectrum also shows that some of these singlets have shoulders, indicating the presence of other, overlapping singlets. The *N*-methyl region also shows overlapping singlets, with at least 12 distinct singlets visible. Taken together, the appearance of these resonances supports the conclusion that **16** adopts a number of the orientations shown in Scheme 7. Because the peaks overlap, it is not possible to count the exact number of orientations for **16**. At a minimum **16** assumes three of the eight

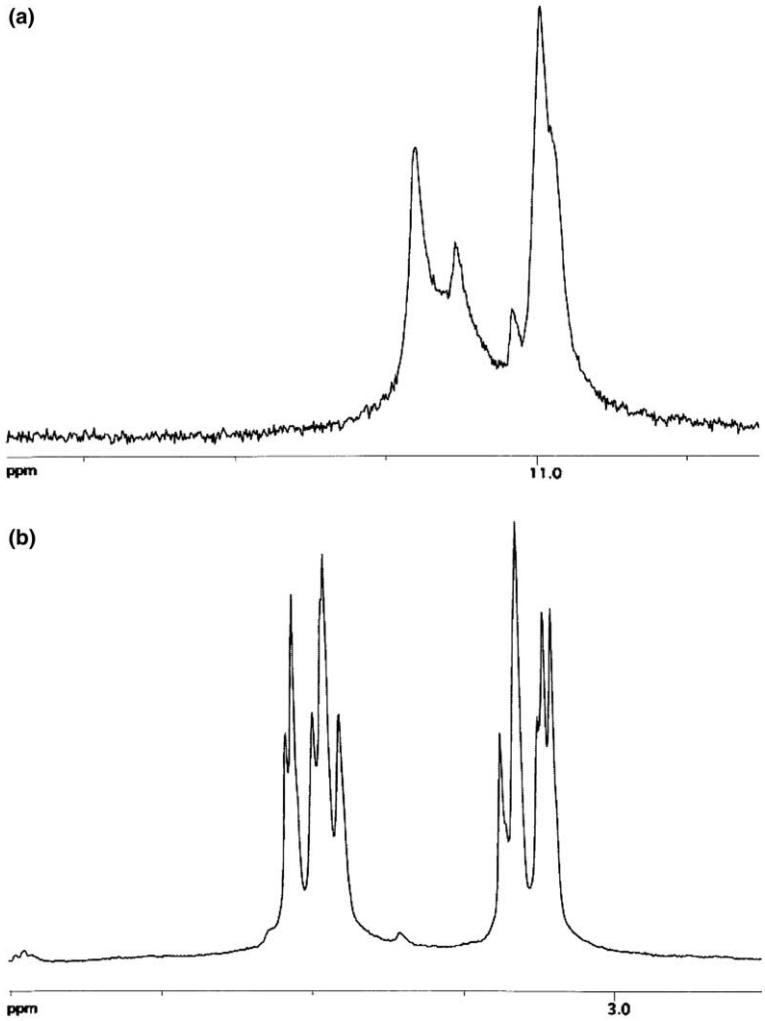


Fig. 1. (a) The region between 10.7 and 11.7 ppm in the ^{1}H NMR spectrum of **16** in $CDCl_3$. The peaks in this region arise from the terminal alkyne hydrogens. (b) The region between 2.8 and 3.8 ppm in the ^{1}H NMR spectrum of **16** in $CDCl_3$. The peaks in this region arise from the *N*-methyl hydrogens on the dmtc groups.

orientations shown in Scheme 7; it is possible that **16** assumes more than three of these orientations.

Inspection of a Dreiding model of **2** supports this conclusion. Compound **2** can adopt conformations in which the two alkynes are parallel to each other and situated approximately 6.5 Å apart. The model shows that this can occur if the two alkynes are aligned with each other (leading to the *syn*-isomers I, J, M and N shown in Scheme 7) or if the alkynes are not aligned with each other (leading to the *anti*-isomers A, B, E and F shown in Scheme 7). The model indicates that none of the eight possible orientations for **16** can be ruled out.

2.4. Cyclization of 3 with $W(CO)_3(dmtc)_2$

Compound **3**, the dialkynylalanine dipeptide, was reacted with $W(CO)_3(dmtc)_2$ under high dilution conditions in an effort to form the cyclic dipeptide, **17** (Scheme 8). As with the similar reactions of **1** and **2**, addition of the $W(CO)_3(dmtc)_2$ to a refluxing, 1 mM solution of **3** in MeOH initially generated a light green solution, which on further heating turned yellow. Workup of the reaction and analysis by TLC showed the formation of one major yellow band. This compound was isolated and purified by flash chromatography. Analysis of the amorphous, yellow solid showed it to be the desired product, **17**. The ESMS produced a series of peaks centered around 726 *m*/*z*, which match the peaks expected for the M + Na ion for **17**. The ^{1}H NMR spectrum also possessed all the resonances for the hydrogens expected in **17**, including the alkyne hydrogens at 11 ppm and the *N*-methyl hydrogens from the dithiocarbamates located in the 3.0–3.5 ppm region, see Scheme 8.

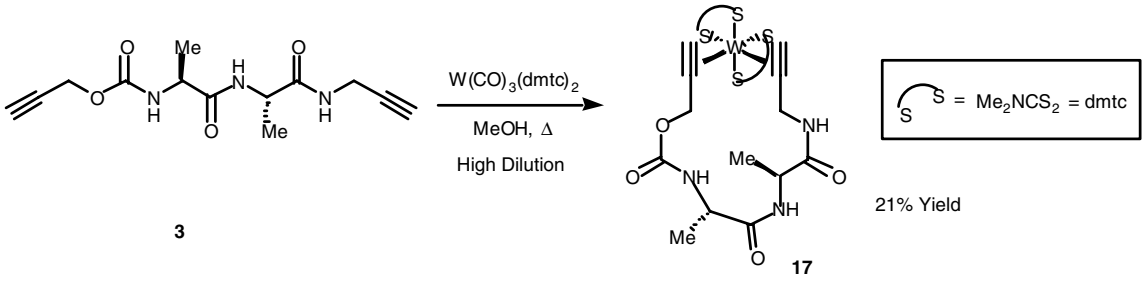
Because there are two stereochemical orientations available to the dithiocarbamate ligands, and because the two alkyne ligands can be *syn* or *anti* with respect to each other, and because there are two ways to orient the peptide around the tungsten, like **16** there are eight possible isomers open to metallacyclicpeptide **17**. The possible isomers of **17** are shown in Scheme 9. Four of these isomers have one of the dithiocarbamate stereochemistries (Q, R, S and T), while the other four isomers have the opposite dithiocarbamate stereochemistry (U, V, W and X). Four of the isomers have the two alkynes aligned in a *syn*-orientation (S, T, W and X), while the other four have the two alkynes arranged in the anti-orientation (Q, R, U and V). Finally, four of the isomers have the peptide in one orientation (Q, S, U and W), while the other four isomers have the opposite peptide orientation (R, T, V and X).

Like **16**, the conformational behavior of metallacyclicpeptide **17** can be assessed by examination of the alkyne hydrogen and *N*-methyl resonances in the ^{1}H NMR spectrum. These two regions are shown in Fig. 2(a) and (b), respectively. The alkyne hydrogen region shows at least 10 different singlets (more signals than seen for **16** (Fig. 1(a))), indicating that **17** adopts a large number of the isomers shown in Scheme 9. The *N*-methyl region for **17** closely resembles the *N*-methyl region for **16** (Fig. 1(b)), except for the addition of several small singlets in the spectrum of **17**. The additional signals seen for **17** compared to **16** suggests that **17** populates more of its possible isomeric forms than does **16**. At a minimum **17** assumes three of the orientations shown in Scheme 9; it also is possible that **17** assumes all eight of the orientations shown in Scheme 9.

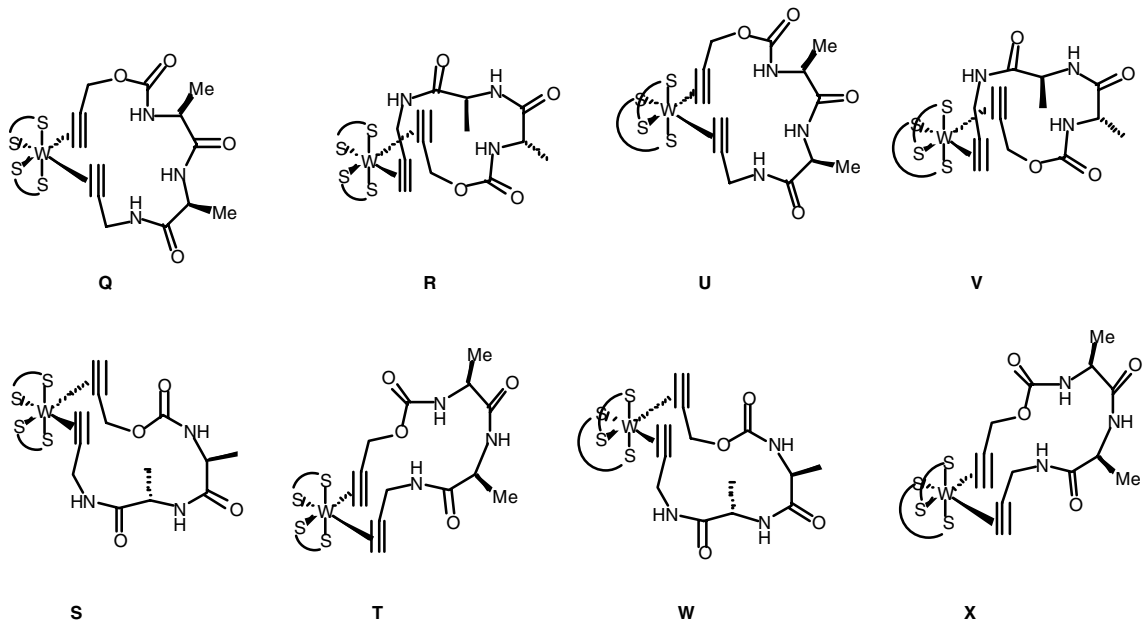
2.5. Variable temperature NMR

To explore the conformational flexibililty of **16** and **17**, their ^{1}H NMR spectra were recorded in d_6-DMSO at temperatures ranging from 21 to 90 °C. Recording the spectra in d_6-DMSO, an aggressive hydrogen bond acceptor solvent, should break up any intramolecular hydrogen bonding interactions, if there are any, in **16** and **17**. Based on the literature of bis(alkyne) complexes of molybdenum and tungsten [5a] raising the temperature should allow for interconversion between the isomers of **16** and **17** and a simplification of their NMR spectra.

The ^{1}H NMR spectra of **16** and **17** in d_6-DMSO at 21 °C are nearly identical to their spectra in $CDCl_3$ at 21 °C. The spectra in d_6-DMSO show multiple peaks for each resonance. Also, the chemical shifts of each resonance are nearly identical in both d_6-DMSO and $CDCl_3$. This indicates that the solution structures of **16** and **17** are essentially the same in both solvents and do not possess any intramolecular hydrogen bonds.



Scheme 8.



Scheme 9.

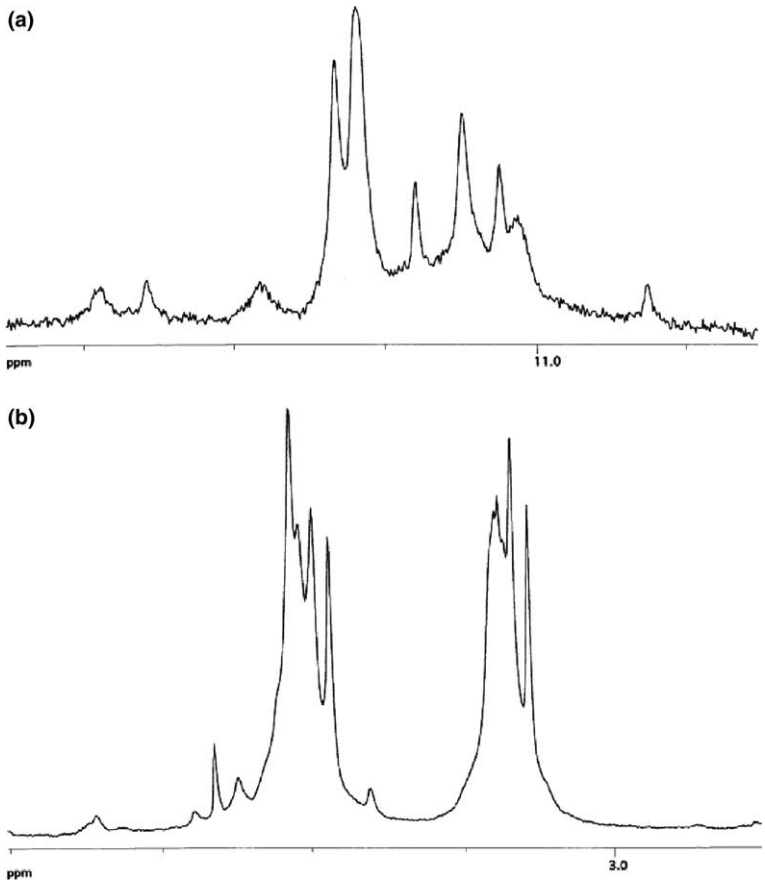


Fig. 2. (a) The region between 10.7 and 11.7 ppm in the ^{1}H NMR spectrum of **17** in $CDCl_3$. The peaks in this region arise from the terminal alkyne hydrogens. (b) The region between 2.8 and 3.8 ppm in the ^{1}H NMR spectrum of **17** in $CDCl_3$. The peaks in this region arise from the *N*-methyl hydrogens on the dmtc groups.

The behavior of **16** and **17** in d_6-DMSO differ as the temperature is raised. With **17**, the spectrum simplifies, with the alkyne hydrogens coalescing to one singlet somewhere between 60 and 70 °C. Coalescence in this temperature range is similar to the coalescence temperatures observed for acyclic bis(alkyne) complexes of molybdenum [5a]. In contrast, the spectrum of **16** does not show any simplification, even when the temperature of the solution is raised to 90 °C; in addition, heating of **16** to 90 °C leads to significant decomposition of the sample. These results show that the smaller ring in **16** is tightly confined and is unable to easily switch from one conformation to another. This indicates that the isomers formed in the synthesis of **16** are kinetic products. A Dreiding model of **2** in which the two alkynes are held parallel to each other and spaced 6.5 Å apart does show that the molecule has little or no conformational freedom. With the larger ring found in **17** comes more conformational freedom. A Dreiding model of **3** in which the two alkynes are held parallel to each other and spaced 6.5 Å apart shows that this molecule will have more freedom of motion when complexed to the tungsten. This is the likely reason why the peaks in the ^{1}H NMR spectrum of **17** in d_6-DMSO coalesce between 60 and 70 °C, but the same peaks in **16** do not.

2.6. Summary

The results from this study show that metallacyclicpeptides can be obtained by reaction of $W(CO)_3(dmtc)_2$ with a peptide bearing alkyne groups at both the N- and C-termini. Limitations on the ability to cyclize reside in dialkynes that are shorter than a dialkynylamino acid. The alkyne group can readily be appended at the N-terminus by reaction of the peptide with propargylchloroformate, while an alkyne group can be readily appended at the C-terminus by acylation of the carboxyl group with propargylamine hydrochloride using a carbodiimide coupling reagent. The metallacyclicpeptides studied here (**16** and **17**) both assume multiple conformations in solution. The two metallacyclicpeptides differ in their ability to interconvert between conformational isomers at higher temperatures; **17** can interconvert between the isomers available to it, while **16** appears unable to interconvert.

3. Experimental

3.1. General procedures

Boc–Ala–OSu and Boc–Ala–Ala–OH were purchased from Bachem. Propargylchloroformate and propargylamine hydrochloride were purchased from Aldrich. DIEA and EDC were purchased from Acros Organics. $CDCl_3$ and d_6-DMSO were purchased from Cambridge Isotope Labs. Silica gel for flash chromatography was purchased from Silicycle. NMR spectra were obtained on a GE Omega 300 instrument. Electrospray mass spectra were obtained on a LCQ APCI/Electrospray LC MS-MS. Samples for mass spectral analysis were dissolved in MeOH (approximately 1 mg/mL) in borosilicate glass test tubes.

3.2. Preparation of *1*

To a stirred suspension of 300 mg (3.28 mmol, 1.0 equiv.) of propargylamine hydrochloride in 30 mL CH_2Cl_2 was added 2.17 mL (13.1 mmol, 4.0 equiv.) of DIEA. Once all the propargylamine hydrochloride dissolved the solution was treated with 0.257 mL (3.11 mmol, 1.0 equiv.) of propargylchlorformate. After stirring at 23 °C for 1 h the solvents were evaporated and the residue redissolved in 30 mL EtOAc, transferred to a separatory funnel and washed: 3×25 mL 1 M HCl, 3×25 mL saturated $NaHCO_3$ and 1×25 mL brine. The EtOAc layer was dried ($MgSO_4$), filtered and evaporated to yield 254 mg (64%) of pure **1** as a white solid: m.p. 35–38 °C; TLC, R_f 0.55 (1:1 EtOAc/hexanes); ^{1}H NMR ($CDCl_3$) δ 5.40 (1H, br s), 4.72 (2H, d, $J = 2.4$ Hz), 4.00 (2H, dd, $J = 2.4$, 5.4 Hz), 2.53 (1H, t, $J = 2.4$ Hz), 2.28 (1H, t, $J = 2.4$ Hz).

3.3. Attempted cyclization of *1*; preparation of *13*, *14* and *15*

A 1000 mL, 3-neck, round-bottom flask equipped with a stir bar, an addition funnel and a reflux condenser was placed under an N_2 atmosphere. To the flask was added a degassed solution of **1** in 450 mL MeOH. To the addition funnel was added a degassed solution of $W(CO)_3(dmtc)_2$ [8] in 75 mL CH_2Cl_2. The MeOH solution was brought to reflux and the $W(CO)_3(dmtc)_2$ solution was added to the flask dropwise over the course of 1 h. After 2 h at reflux the solution had turned a light yellow color. Heating was halted and the solvents evaporated. TLC analysis of the crude product showed three major yellow bands. The crude product was subjected to flash chromatography (2 cm silica gel column, 10 mL fractions, 3:2 EtOAc/hexanes eluant). After 60 fractions had been collected the eluant was changed to pure EtOAc, and an additional 80 fractions were collected. From these fractions **13** (fractions 41–55, 61 mg, 15%), **14** (fractions 119–126, 28 mg, 7%) and **15** (fractions 81–88, 7 mg, 2%) were isolated pure.

13: amorphous yellow solid; TLC, R_f 0.45 (1:1 EtOAc/hexanes); ESMS, M + Na ion theoretical isotope pattern calculated for $WC_{20}H_{26}O_4N_4S_4Na$ [9]: 717 (0.3%), 718 (0.1%), 719 (65.7%), 720 (53.0%), 721 (100%), 722 (31.7%), 723 (90.6%), 724 (23.8%), 725 (17.6%), 726 (4.1%), 727 (1.6%), 728 (0.3%), 729 (0.1%). Found: 717 (1.5%), 718 (1.1%), 719 (72.9%),

720 (61.1%), 721 (100%), 722 (33.9%), 723 (89.6%), 724 (21.5%), 725 (19.1%), 726 (4.3%), 727 (1.7%), 728 (1.3%).

14: amorphous yellow solid; TLC, R_f 0.12 (1:1 EtOAc/hexanes); ESMS, M + Na ion theoretical isotope pattern calculated for $W_2C_{26}H_{38}O_4N_6S_8Na$ [9]: 1139 (0.2%), 1140 (0.1%), 1141 (19.1%), 1142 (27.4%), 1143 (64.8%), 1144 (53.3%), 1145 (100.0%), 1146 (65.6%), 1147 (91.5%), 1148 (39.8%), 1149 (51.9%), 1150 (18.7%), 1151 (14.8%), 1152 (4.7%), 1153 (2.5%), 1154 (0.7%), 1155 (0.3%), 1156 (0.1%). Found: 1139 (0.8%), 1140 (2.1%), 1141 (25.5%), 1142 (29.4%), 1143 (67.0%), 1144 (55.2%), 1145 (100.0%), 1146 (64.9%), 1147 (86.7%), 1148 (42.4%), 1149 (49.6%), 1150 (15.9%), 1151 (14.0%), 1152 (2.6%), 1153 (1.1%), 1154 (0.5%), 1155 (0.4%), 1156 (1.8%).

15: amorphous yellow solid; TLC, R_f 0.33 (1:1 EtOAc/hexanes); ESMS, M + Na ion theoretical isotope pattern calculated for $W_2C_{33}H_{45}O_6N_7S_8Na$ [9]:1276 (0.2%), 1277 (0.1%), 1278 (18.2%), 1279 (27.6%), 1280 (64.1%), 1281 (56.1%), 1282 (100.0%), 1283 (70.8%), 1284 (93.1%), 1285 (45.6%), 1286 (53.3%), 1287 (22.2%), 1288 (15.9%), 1289 (5.8%), 1290 (2.8%), 1291 (0.9%), 1292 (0.3%), 1293 (0.1%); Found: 1276 (2.3%), 1277 (2.0%), 1278 (19.6%), 1279 (29.0%), 1280 (64.3%), 1281 (56.9%), 1282 (100.0%), 1283 (67.1%), 1284 (89.3%), 1285 (41.3%), 1286 (48.0%), 1287 (19.1%), 1288 (15.1%), 1289 (4.9%), 1290 (2.6%), 1291 (1.4%), 1292 (1.3%), 1293 (0.8%).

3.4. Preparation of 7

To a suspension of 0.538 g (5.88 mmol, 1.6 equiv.) of propargylamine hydrochloride in 35 mL CH_2Cl_2 was added 8.0 mL (46 mmol, 12 equiv.) of DIEA. After stirring for 5 min the solution was treated with 1.08 g (3.77 mmol, 1.0 equiv.) of Boc–Ala–OSu (**6**). After 18 h the solvents were evaporated and the residue redissolved in 50 mL EtOAc, transferred to a separatory funnel and washed: 3×50 mL 1 M HCl, 3×50 mL saturated $NaHCO_3$, and 1×50 mL brine. The EtOAc layer was dried ($MgSO_4$), filtered, and evaporated to yield 717 mg (81%) of pure **7** as a white solid: TLC, R_f 0.66 (1:2 EtOAc/hexanes); ^{1}H NMR ($CDCl_3$) δ 6.43 (1H, br s), 4.92 (1H, br s), 4.16 (1H, m), 4.05 (2H, m), 2.23 (1H, t, J = 2.4 Hz), 1.46 (9H, s), 1.37 (3H, d, J = 6.8 Hz).

3.5. Preparation of 2

A solution of 717 mg (3.06 mmol, 1.0 equiv.) of **7** dissolved in 8 mL CH_2Cl_2 and chilled to 0 °C was added 0.5 mL anisole and 8 mL CF_3CO_2H. The resulting solution stirred for 1 h while warming to 23 °C. The solvents were evaporated in vacuo. The clear oil that remained (the trifluoroacetate salt of **8**) was redissolved in 30 mL CH_2Cl_2 and treated sequentially with 8.0 mL (46 mmol, 15 equiv.) DIEA and 2.0 mL (24 mmol, 8 equiv.) of propargylchloroformate. After 18 h the solvents were evaporated and the residue redissolved in 50 mL EtOAc, transferred to a separatory funnel and washed: 3×50 mL 1 M HCl, 3×50 mL saturated $NaHCO_3$ and 1×50 mL brine. The EtOAc layer was dried ($MgSO_4$), filtered and evaporated to yield the crude product. TLC (EtOAc) showed the crude product to be impure, so it was subjected to flash chromatography (3 cm silica gel column, 20 mL fractions, eluant 2:1 hexanes/EtOAc). Evaporation of fractions 31–44 provided 428 mg (67%) of pure **2** as a white solid: TLC, R_f 0.74 (EtOAc); ^{1}H NMR ($CDCl_3$) δ 6.58 (1H, br s), 5.58 (1H, br s), 4.76 (2H, s), 4.31 (1H, m), 4.09 (2H, dd, J = 7.4, 2.4 Hz), 2.54 (1H, t, J = 2.4 Hz), 2.28 (1H, t, J = 2.4 Hz), 1.45 (3H, d, J = 6.8 Hz).

3.6. Cyclization of 2; preparation of 16

A 500 mL, three-neck, round-bottom flask equipped with a stir bar, an addition funnel and a reflux condenser was placed under an N_2 atmosphere. To the flask was added a degassed solution of **2** in 270 mL MeOH. To the addition funnel was added a degassed solution of $W(CO)_3(dmtc)_2$ [8] in 32 mL CH_2Cl_2. The MeOH solution was brought to reflux and the $W(CO)_3(dmtc)_2$ solution was added to the flask dropwise over the course of 1 h. After 18 h at reflux the solution had turned a light yellow color. Reflux was halted and the solvents evaporated. TLC analysis of the crude product showed one major yellow band. The crude product was subjected to flash chromatography (2 cm silica gel column, 10 mL fractions, EtOAc eluant). The desired product, **16**, eluted pure in fractions 29–38. These fractions were pooled and evaporated to yield 73 mg (29%) of pure **16** as an amorphous, yellow solid: TLC, R_f 0.20 (EtOAc); ^{1}H NMR d 11.3–10.9 (2H, m), 8.4–8.2, 7.5–7.3, 6.7–6.5, 6.0–5.7, 5.4–4.9 (4H, m), 4.4–3.9 (3H, m), 3.5–3.3 (6H, m), 3.2–3.0 (6H, m), 1.5–1.3 (3H, m); ESMS: M + Na theoretical isotope pattern for $WC_{16}H_{24}N_4S_4O_3Na$ [9]: 651 (0.3%), 652 (0.1%), 653 (67.3%), 654 (51.4%), 655 (100.0%), 656 (27.9%), 657 (91.3%), 658 (20.3%), 659 (16.8%), 660 (3.4%), 661 (1.4%), 662 (0.2%), 663 (0.1%); Found: 651 (0.6%), 652 (1.3%), 653 (75.6%), 654 (53.5%), 655 (100.0%), 656 (25.0%), 657 (93.1%), 658 (18.0%), 659 (13.9%), 660 (3.0%), 661 (2.4%), 662 (0.8%), 663 (0.1%).

3.7. Preparation of 10

Four hundred and fifty-eight milligrams (1.76 mmol, 1.0 equiv.) of Boc–Ala–Ala–OH (**9**) and 71 mg (1.78 mmol, 1.0 equiv.) of propargylamine hydrochloride was suspended in 17 mL CH_2Cl_2. To the suspension was then added 0.178 mL (1.08 mmol, 1.40 equiv.) of DIEA and and 152 mg (0.791 mmol, 1.03 equiv.) of

EDC. After stirring for 18 h at 23 °C the solvents were evaporated and the residue redissolved in 50 mL EtOAc. The EtOAc solution was transferred to a separatory funnel and washed: 3 × 50 mL 1 M HCl, 3 × 50 mL saturated $NaHCO_3$, and 1 × 50 mL brine. The EtOAc was dried ($MgSO_4$), filtered, and evaporated to yield 141 mg (27%) of pure **10** as a white solid: TLC, R_f 0.31 (1:1 EtOAc/hexane); ^1H NMR δ 7.18 (1H, br s), 6.78 (1H, br s), 5.17 (1H, d, $J = 5.9$ Hz), 4.57 (1H, m), 4.20–3.90 (5H, m), 2.21 (1H, t, $J = 2.4$ Hz), 1.48 (9H, s), 1.44 (3H, d, $J = 6.8$ Hz), 1.40 (3H, d, $J = 7.3$ Hz).

3.8. Preparation of 3

A solution of 141 mg (0.475 mmol, 1.0 equiv.) of **10** dissolved in 5 mL CH_2Cl_2 and chilled to 0 °C was added 0.5 mL anisole and 5 mL CF_3CO_2H. The resulting solution stirred for 1 h while warming to 23 °C. The solvents were evaporated in vacuo. The clear oil that remained (the trifluoroacetate salt of **11**) was redissolved in 10 mL CH_2Cl_2 and treated sequentially with 1.26 mL (7.24 mmol, 15 equiv.) DIEA and 0.313 mL (3.21 mmol, 6.8 equiv.) of propargylchloroformate. After 18 h the solvents were evaporated and the residue redissolved in 50 mL EtOAc, transferred to a separatory funnel and washed: 3 × 50 mL 1M HCl, 3 × 50 mL saturated $NaHCO_3$, and 1 × 50 mL brine. The EtOAc layer was dried ($MgSO_4$), filtered, and evaporated to yield the crude product. TLC (EtOAc) showed the crude product to be impure, so it was subjected to flash chromatography (2 cm silica gel column, 10 mL fractions, eluant 2:1 EtOAc/hexanes). Evaporation of fractions 39–46 provided 41 mg (31%) of pure **3** as a white solid: TLC, R_f0.24 (2:1 EtOAc/hexanes); ^1H NMR ($CDCl_3$) δ 6.79 (1H, br s), 6.60 (1H, m), 5.49 (1H, d, $J = 6.3$ Hz), 4.8–4.6 (2H, m), 4.49 (1H, pentet, $J = 6.8$ Hz), 4.3–3.9 (3H, m), 2.49 (1H, t, $J = 2.4$ Hz), 2.24 (1H, t, $J = 2.4$ Hz), 1.41 (6H, d, $J = 6.8$ Hz).

3.9. Cyclization of 3; preparation of 17

A 500 mL, three-neck, round-bottom flask equipped with a stir bar, an addition funnel and a reflux condenser was placed under an N_2 atmosphere. To the flask was added a degassed solution of 53 mg (0.19 mmol, 1.0 equiv.) of **3** in 150 mL MeOH. To the addition funnel was added a degassed solution of 97 mg (0.19 mmol, 1.0 equiv.) of $W(CO)_3(dmtc)_2$ [8] in 15 mL CH_2Cl_2. The MeOH solution was brought to reflux and the $W(CO)_3(dmtc)_2$ solution was added to the flask dropwise over the course of 1 h. After 18 h at reflux the solution had turned a light yellow color. Reflux was halted and the solvents evaporated. TLC analysis of the crude product showed one major yellow band. The crude product was subjected to flash chromatography (2 cm silica gel column, 10 mL fractions, EtOAc eluant). The desired product, **17**, eluted pure in fractions 26–43. These fractions were pooled and evaporated to yield 28 mg (21%) of pure **17** as an amorphous, yellow solid: TLC, R_f 0.18 (EtOAc); ^1H NMR 11.7–10.9 (2H, m), 8.0–3.8 (9H, m), 3.6–3.3 (6H, m), 3.2–3.0 (6H, m), 1.5–1.2 (6H, m); ESMS M + Na theoretical isotope pattern [9]: 722 (0.3%), 723 (0.1%), 724 (65.9%), 725 (52.8%), 726 (100.0%), 727 (31.1%), 728 (90.8%), 729 (23.3%), 730 (17.5%), 731 (4.0%), 732 (1.6%), 733 (0.3%), 734 (0.1%); Found: 722 (0.8%), 723 (0.9%), 724 (73.4%), 725 (55.4%), 726 (100.0%), 727 (31.4%), 728 (92.2%), 729 (19.2%), 730 (16.9%), 731 (4.3%), 732 (2.1%), 733 (0.4%), 734 (0.9%).

Acknowledgments

This work was supported by a grant from the National Science Foundation (NSF-RUI CHE-0305325), and from a Student Research Assistant Grant from Trinity College. We thank Profs. Nils Metzler-Nolte and Margaret Harding for their helpful and insightful questions at the Second International Symposium on Bioorganometallic Chemistry, Zurich, Switzerland, July, 2004.

References

[1] K. Severin, R. Bergs, W. Beck, Angew. Chem., Int. Ed. Engl. 37 (1998) 1635.
[2] J.L. Templeton, Adv. Organomet. Chem. 29 (1989) 1.
[3] T.P. Curran, A.L. Grant, R.A. Lucht, J.C. Carter, J. Affonso, Org. Lett. 4 (2002) 2917.
[4] J.L. Templeton, R.S. Herrick, J.R. Morrow, Organometallics 3 (1984) 535.
[5] (a) R.S. Herrick, J.L. Templeton, Organometallics 1 (1982) 842;
(b) J.R. Morrow, T.L. Tonker, J.L. Templeton, J. Am. Chem. Soc. 107 (1985) 5004.
[6] (a) W. Henderson, B.K. Nicholson, L.J. McCaffrey, Polyhedron 17 (1998) 4291;
(b) J.C. Traeger, Int. J. Mass Spectrom. 200 (2000) 387.
[7] X. Hua, A. von Zelewsky, Inorg. Chem. 34 (1995) 5791.
[8] S.J.N. Burgmayer, J.L. Templeton, Inorg. Chem. 24 (1985) 2224.
[9] Theoretical isotope patterns were calculated using a program available at a website provided by the University of Sheffield. Available from: http://www.shef.ac.uk/chemistry/chemputer/.