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Total Synthesis of Pumiliotoxin 341A

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Introduction

Pumiliotoxins comprise one of the most ubiquitous and largest classes of alkaloids isolated from the skin extracts of poison frogs.[14] Charles Myers and John Daly originally isolated pumiliotoxins from the brightly colored Western Columbian poison-dart frog species, *Dendrobates pumilio*. Since then, they have been extracted from nearly all alkaloid-containing frog species inhabiting Central and South America, Australia, and Madagascar.[6] In essence, pumiliotoxins are 6-alkylideneindolizidine heterocycles with a methyl and tertiary hydroxyl group at C8. They are divided into separate subclasses based upon the type of alkylidene side chain contained within each pumiliotoxin.[14] The exact nature of this side chain determines the type of biological associated with the pumiliotoxin.[7]

When Myers and Daly initially discovered this unique group of natural products, they also succeeded in showing that pumiliotoxins display various cardiotonic and myotonic activities. Pumiliotoxins accomplish this by positively modulating sodium channels and indirectly stimulating inosital phosphate formation. This biological activity has made these alkaloids an important subject of study contributing to the development of new cardiotonics with minimal side effects.[6]

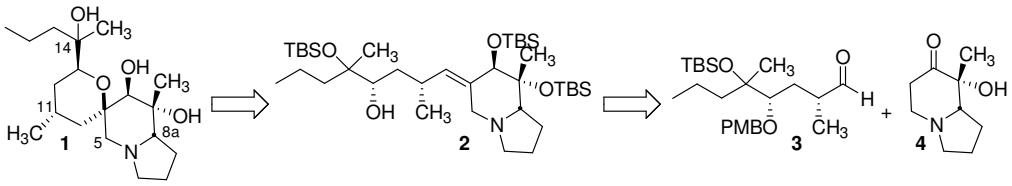
Although almost all the pumiliotoxin side chains are linear variations, a single pumiliotoxin exists that contains a cyclized side chain - pumiliotoxin 341A. This pumiliotoxin is exceptionally unique because the cyclized side chain forms a pyranose ring, which results in an additional stereocenter within its indolizidine core. Unfortunately, this alkaloid rarely occurs in frog skin extracts. Only 1 mg

has been isolated from the Ecuadoran frog species, *Epipedobates tricolor*.[14] This limited quantity has prevented further, important biological exploration of this distinctive pumiliotoxin.

Currently, the overall structure of pumiliotoxin 341A is known due to NMR methods. However, the stereochemistry (absolute and relative) remains undetermined. Therefore, we would like to synthesize this natural product in order to establish the structure and explore the biological activity. Success in these two endeavors will allow this compound to serve as a model for the development of a new cardiotonic and/or myotonic agent.

A retrosynthetic analysis of pumiliotoxin 341A **1** is shown below in Figure 1. The oxygen-carbon bond of the pyranose ring breaks to form the alkene intermediate **2** with a linear side chain, which we anticipate to recyclize with a mercury catalyst. Alkene **2** separates to form two core components of pumiliotoxin 341A - the aldehyde coupling partner **3** and the indolizidine ring **4**. We expect to combine these two fragments using an aldol reaction.

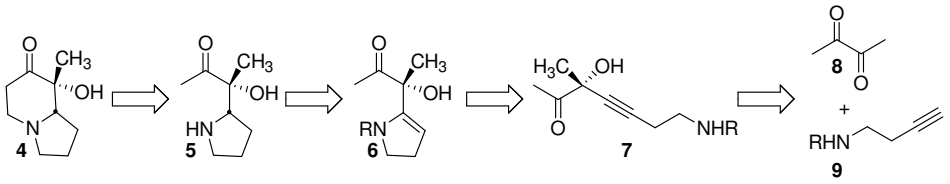
Figure 1. Retrosynthesis of Pumiliotoxin 341A



In this report, we will focus on the synthesis of the indolizidine ring **4** and place special emphasis on forming the correct stereochemistry of the C8a stereocenter. A retrosynthetic analysis of **4** is shown below in Figure 2. We expect to derive **4** from a rhodium-catalyzed alkyne addition to a dicarbonyl, a reaction currently being developed by our group. We anticipate breaking the

bond between nitrogen and C5 of **4** using a Mannich reaction, which results in the formation of ketone **5**. Afterwards, the pyrrolidine ring of **6** is synthesized by performing an intramolecular cyclization of the protected amine group of alkyne **7** onto the corresponding triple bond. We expect to form **7** by performing the rhodium-catalyzed alkyne addition (mentioned above) between 2,3-butanedione **8** and the protected amine **9**.

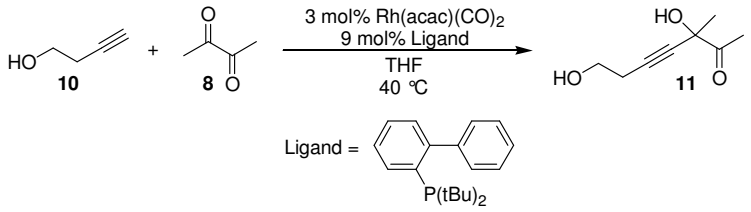
Figure 2. Retrosynthesis of Indolizidine Core



Results and Discussion

As mentioned previously, we will use the rhodium-catalyzed addition of an alkyne to 2,3-butanedione **8** in our synthesis of indolizidine **4**. Using 3-butyne-1-ol **10** as the alkyne, 2,3-butanedione **8** as the electrophile, and dicarbonylacetylacetonato-rhodium (I) with 2-(di-t-butylphosphino)-biphenyl to form the catalyst, we first tried a model system (Scheme 1). Adduct **11** was obtained in 94% yield, which confirmed the competency of this addition reaction.

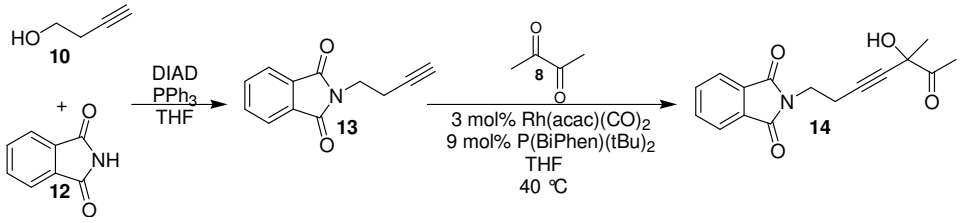
Scheme 1



Based upon this result, we thought it likely that the reaction would also work with a protected aminoalkyne. In order to prepare the desired aminoalkyne, we

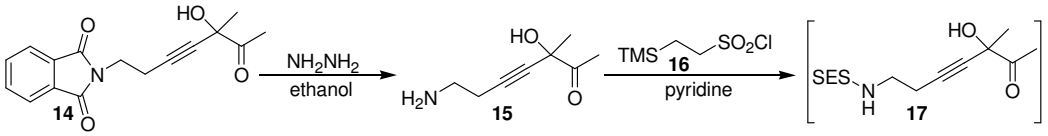
subjected **10** and phthalimide **12** to Mitsunobu conditions to form the protected amine **13**, which was obtained in 96% yield (Scheme 2).[8] Alkyne **13** was then added to 2,3-butanedione **8** under the same conditions set forth in the model system with **10**. The rhodium-catalyzed alkyne addition with amine **13** was successful and we formed adduct **14** in 60% yield.

Scheme 2



Afterwards, deprotection of **14** using hydrazine produced ketone **15** (Scheme 3). Although the deprotection was successful, the high polarity of **15** made it very difficult to purify. Despite the impurities contained within **15**, we still attempted to perform a SES-Cl (**16**) reprotection of its amine group. However, the desired SES-protected amine **17** was not detected in the ^{1}H NMR spectrum of the reaction mixture. As a result, we concluded that the inability to purify **15** made the ketone too difficult to work with.

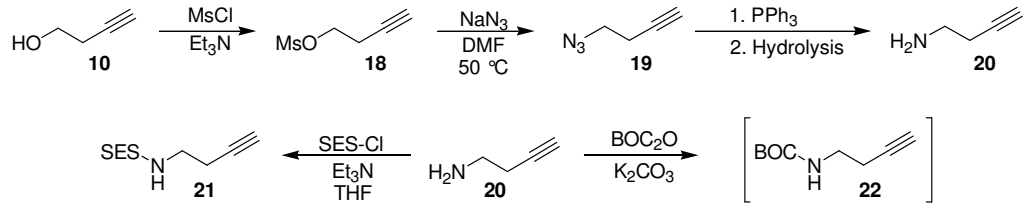
Scheme 3



Therefore, we decided to make a different aminoalkyne, **20** (Scheme 4). The hydroxyl group on **10** was activated with methanesulfonyl chloride to form mesylate **18** in 86% yield. The mesylate was displaced in an S_N2 reaction by azide to produce alkyne **19**. Due to its instability, **19** was immediately reduced to

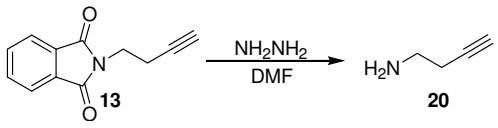
aminoalkyne **20**. This monosubstituted amine was then protected with 2-(trimethylsilyl)ethanesulfonyl chloride (SES-Cl) to form aminoalkyne **21** in 7% yield. Since the yield was so poor, we decided to try tert-butyl oxy carbonyl (BOC) as an alternate protecting group in hopes of achieving a higher yield. Therefore, **20** was suspended in a solution of BOC anhydride and potassium carbonate in order to form amine **22** but the desired product was not detected in the crude ^{1}H NMR spectrum.

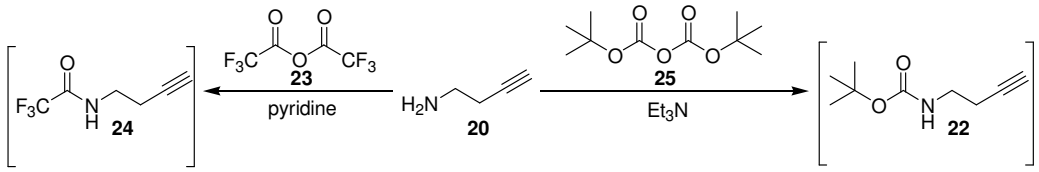
Scheme 4



The non-optimal and unsuccessful protection of aminoalkyne **20** led us to believe that the mesylate pathway for its formation possibly results in too many impurities. As a result, a different methodology was used to obtain the same aminoalkyne **20** (Scheme 5). The protected amine **13**, previously prepared as described above (see Scheme 2), was deprotected with hydrazine to form **20**. Trifluoroacetic anhydride **23** and BOC anhydride **25** were used in separate attempts to protect **20** but both protections failed. Neither desired product, **24** and **22** respectively, was detected in the corresponding ^{1}H NMR spectra.

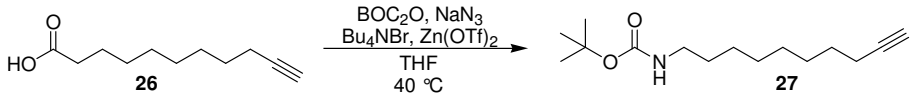
Scheme 5





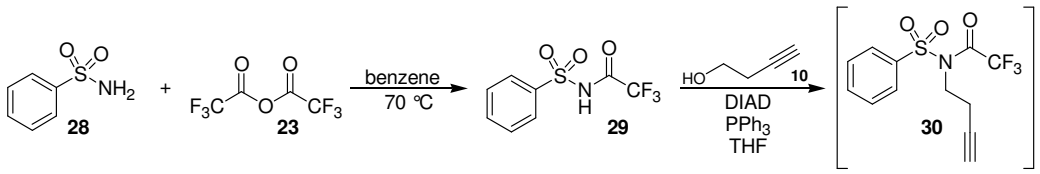
After these failed protections, we decided to make a completely different amine. However, we still wanted to use BOC as the protecting group. In one step, undecynoic acid **26** could be converted to the BOC-protected aminoalkyne **27** yield using the following reagents: BOC anyhydride, sodium azide, tetrabutyl ammonium bromide, and zinc triflate (Scheme 6).[12] The obtained yield for **27** was 22%. Due to this unfavorable yield, this approach was discarded and the formation of yet another aminoalkyne was initiated.

Scheme 6



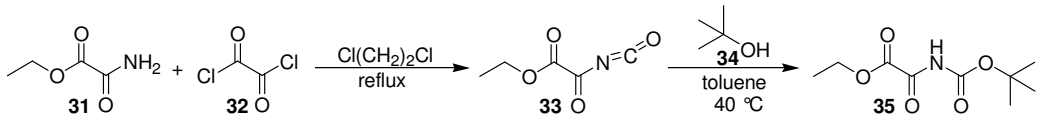
In another approach, we protected the amine functional group of benzenesulfonamide **28** with trifluoroacetic anhydride **23** (Scheme 7). Although the protected sulfonamide **29** was made, the reaction would not go to completion. Separating the starting material from the final product proved to be very difficult and not quite successful. As a result, a crude yield of 55% was obtained for **29**. **29** and 3-butyne-1-ol were then subjected to Mitsunobu conditions in hopes of forming amine **30**, a different aminoalkyne.[8] Unfortunately, the desired product was not detected in the ^{1}H NMR spectrum. The impure mixture of **28** and **29** could have possibly interfered with the formation of **30**. Therefore, this tactic was discarded and the preparation of a different aminoalkyne was re-initiated.

Scheme 7



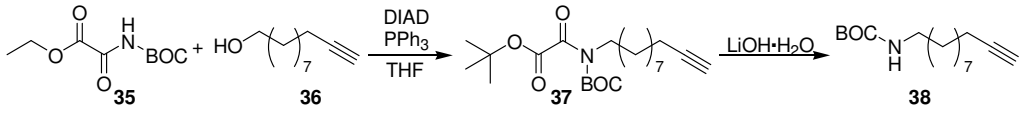
In the new approach, BOC served once again as the protecting group for the desired aminoalkyne. To form a BOC-protected amine nucleophile, ethyl oxamate **31** and oxalyl chloride **32** were reacted in 1,2-dichloroethane to produce isocyanate **33** in 70% yield (Scheme 8).[3] Tert-butyl alcohol **34** was added to isocyanate **33** to form the BOC-protected amine **35** in 95% yield.

Scheme 8



We wanted to use amine nucleophile **35** to ultimately produce the desired protected amine **9** (see Figure 2). To see if this was possible, we first used a model system with 10-undecyne-1-ol **36** and **35**, which were placed under Mitsunobu conditions to form alkyne **37** in 53% yield (Scheme 9). **37** was hydrolyzed with lithium monohydrate to remove its ethyl oxamate group. This produced the desired, longer BOC-protected amine **38** in 73% yield.

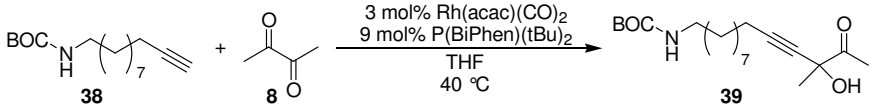
Scheme 9



Having made the protected amine, we wanted to see if BOC was a legitimate protecting group that could be used in the rhodium-catalyzed addition reaction. **38** was added to 2,3-butanedione **8** in the appropriate conditions to produce adduct

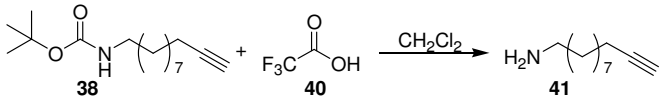
39 in 35% yield (Scheme 10). Based upon this result, we established that BOC was a credible protecting group.

Scheme 10



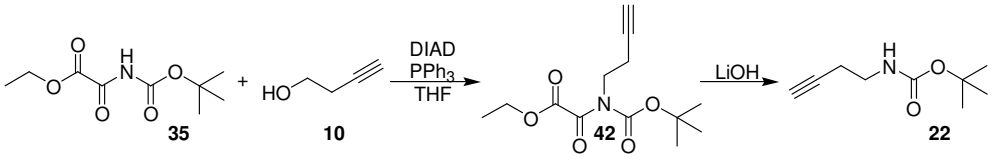
After having reached that conclusion, protected amine **39** was deprotected by removing its BOC group with trifluoroacetic acid **40**. This deprotection formed aminoalkyne **41** in a 74% yield (Scheme 11). However, this was just a crude yield because purification of **41** was very difficult as a result of its high polarity.

Scheme 11



With the success of this model, we hoped that we could follow the same sequence except replace 10-undecyne-1-ol **39** with 3-butyne-1-ol **10** to form a BOC-protected form of amine **9** (see Figure 2). Amine nucleophile **35** was converted to alkyne **42** by subjecting it and 3-butyne-1-ol **10** to Mitsunobu conditions (Scheme 12). This produced **42** in 89% yield. The ethyl oxamate group of **42** was then hydrolyzed with lithium monohydrate to form the BOC-protected aminoalkyne **22** in 82% yield.

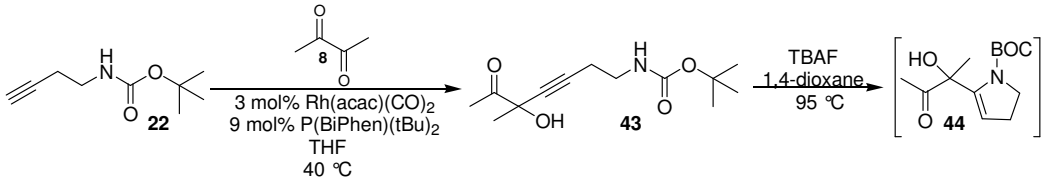
Scheme 12



Aminoalkyne **22** now could be utilized as the protected amine **9** as

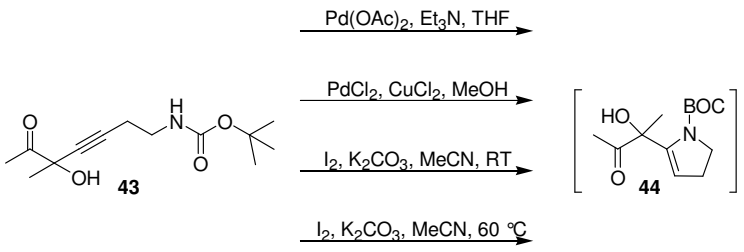
described in the indolizidine core retrosynthetic analysis discussed above (see Figure 2). Alkyne **22** was added to 2,3-butanedione **8** in the rhodium-catalyzed alkyne addition reaction to produce the desired BOC-protected amine **43** in 97% yield (Scheme 13). Attempts were then made to cyclize the amine onto the triple bond. TBAF was used as reported by Jacobi.[9] However, the desired cyclized product **44** was not detected in the ^{1}H NMR spectrum.

Scheme 13



Other cyclization attempts were made but none were successful. The different reaction reagents included palladium acetate with triethylamine, palladium chloride with copper chloride, and iodide and potassium carbonate (Scheme 14). Both the iodide and potassium carbonate reagents were used in two separate reactions set at two different temperatures - room temperature and 60 degrees Celsius. For each cyclization reaction, the desired cyclized product **44** was not detected in any of the ^{1}H NMR spectra.

Scheme 14



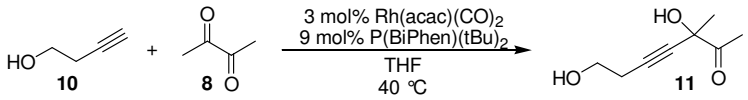
Conclusion

To synthesize the desired indolizidine core **4** of pumiliotoxin 341A **1**,

several attempts were made to form various versions of the protected amine **9**, which would be used in the rhodium-catalyzed alkyne addition reaction. The optimal approach was the route beginning with ethyl oxamate and ending with the formation of aminoalkyne **43**. After the successful synthesis of the protected aminoalkyne, the key cyclization reaction was explored. Unfortunately, this cyclization was too difficult. This may be due to sterics or the poor nucleophilicity of the BOC nitrogen. Future work will include using a more nucleophillic protected amine such as **21**.

Experimental Details

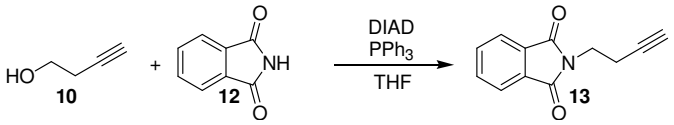
LBC-I-3



Dicarbonylacetylacetonato-rhodium (I) (62 mg, 0.24 mmol) and 2-(di-t-butylphosphino)-biphenyl (215 mg, 0.72 mmol) were combined in a dry test tube under argon. 3-butyne-1-ol (560 mg, 8 mmol), 2,3-butanedione (2.06 g, 24 mmol), and 8 ml anhydrous THF were combined in a second dry test tube under argon. The second test tube was degassed as its contents stirred at room temperature for ten minutes. After thorough stirring, the mixture in the second test tube was placed into the first test tube containing the rhodium and the ligand. The reaction was then placed in a 40-degree Celsius oil bath and stirred for 24 hours. The final reaction mixture was concentrated and the product was purified via a silica column using a solution of 50% ethyl acetate, 50% hexanes as the solvent system. 1.18 g was obtained as a clear oil, giving a 94% yield. TLC R_f= 0.31 (50% ethyl acetate/50% CH_2Cl_2). IR (neat): 3401, 2937, 2250, 1723 cm^{-1}. ^1H

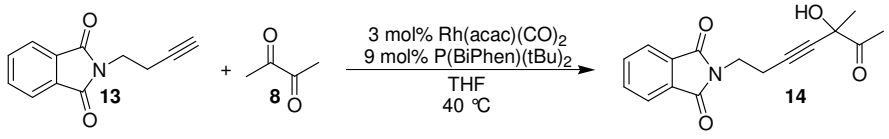
NMR (300 MHz, $CDCl_3$) δ 4.55 (s, 1H), 3.65 (t, *J* = 6.0 Hz, 2H), 3.47 (s, 1H), 2.41 (t, *J* = 6.2 Hz, 2H), 2.33 (s, 3H), 1.52 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.5, 83.8, 81.1, 72.7, 60.6, 27.0, 23.5, 23.1. Anal Calc'd for $C_8H_{12}O_3$: C, 61.52; H, 7.74. Found: C, 61.33; H, 7.70.

LBC-I-26



Triphenylphosphine (11.43 g, 43.59 mmol) and phthalimide (17.49 g, 118.89 mmol) were added to a dry flask followed by 96 ml anhydrous THF. 3-butyne-1-ol (3 ml, 39.63 mmol) was added next; after which the whole flask was placed in an ice bath. Then, diisopropyl-azo-dicarboxylate (8.58 ml, 43.59 mmol) was slowly added dropwise. The reaction was removed from the ice bath, warmed to room temperature, and stirred overnight. It was then concentrated as a white solid. The product was isolated via a silica column using the following graduated solvent system: 20% ethyl acetate, 80% hexanes; 30% ethyl acetate, 70% hexanes; and 40% ethyl acetate, 60% hexanes. 7.56 g was obtained, giving a 96% yield. The spectral data matched those in the literature.[16]

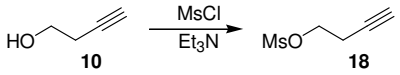
LBC-I-21



Dicarbonylacetylacetonato-rhodium (I) (8 mg, 0.03 mmol), 2-(di-t-butylphosphino)-biphenyl (26.86 mg, 0.09 mmol), and LBC-I-26 (200 mg, 1.0 mmol) were added to a dry test tube under argon. 2,3-butanedione (259 mg, 3.0

mmol) and 1.25 ml anhydrous THF were added to a second dry test tube under argon. The second test tube was degassed as its contents stirred at room temperature for ten minutes. After thorough stirring, the mixture in the second test tube was placed into the first test tube containing the rhodium and the ligand. The reaction was then placed in a 40-degree Celsius oil bath and stirred for 24 hours. The final reaction mixture was concentrated and the product was purified via a silica column using a solution of 50% ethyl acetate, 50% hexanes as the solvent system. 0.17 g was obtained as an off-white solid, giving a 60% yield. Melting point = 84-86 degrees Celsius. TLC R_f = 0.32 (40% ethyl acetate, 60% hexanes). IR (film): 3464.6, 2933.3, 2252.3, 1713.9, 721.7 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 3.97 (s, 1H), 3.85 (t, 2H, J = 6.9 Hz), 2.62 (t, 2H, J = 7.1 Hz), 2.31 (s, 3H), 1.49 (s, 3H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 206.25, 168.34, 134.53, 132.24, 123.68, 82.75, 81.87, 72.78, 36.66, 27.18, 23.54, 19.10. Anal calcd for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.30; N, 4.91. Found: C, 67.04; H, 5.26; N, 4.89.

LBC-I-32

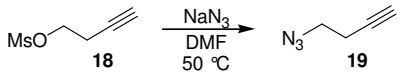


10 **18**

16 ml anhydrous ether added to a flame-dried flask under argon. 3-butyne-1-ol (1.08 ml, 14.27 mmol) and triethylamine (2.11 ml, 15.12 mmol) were added next followed by a slow dropwise addition of methanesulfonyl chloride (1.16 ml, 15.0 mmol). The reaction stirred for 3 hours, after which 5 ml of distilled water were added. The organic layer was washed with 5 ml of distilled water. This was repeated two more times. The organic layer was then dried with magnesium sulfate and concentrated into an oil. 1.81 g was obtained, giving a 86% yield.

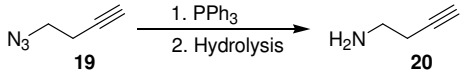
The spectral data matched those in the literature.[17]

LBC-I-36



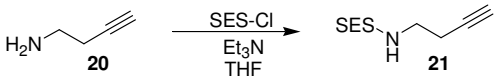
LBC-I-32 (1.80 g, 12.18 mmol) was added to a dry flask under argon. 11 ml distilled DMF was added next and then the flask was placed in a 50-degree Celsius oil bath. This was followed by the addition of sodium azide (2.09 g, 32.17 mmol). The reaction stirred overnight, after which it was cooled to room temperature. 25 ml distilled water were then added. The organic layer was extracted with 25 ml ether. This was repeated once more. The organic extracts were combined, washed with 20 ml distilled water, dried with magnesium sulfate, and concentrated into an oil. The spectral data matched those in the literature.[17]

LBC-I-37



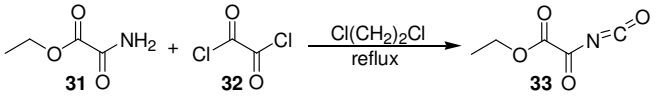
LBC-I-36 (1.16 g, 12.18 mmol) and triphenylphosphine (3.20 g, 12.19 mmol) were added to a dry flask under argon. The reaction stirred for two hours at room temperature. Then, 4 ml distilled water were added and the reaction stirred overnight. The final reaction mixture was vacuum filtered twice and the precipitate was washed with cold n-pentane each time. The product was concentrated into an oil and then distilled for better purification. The spectral data matched those in the literature.[17]

LBC-I-13



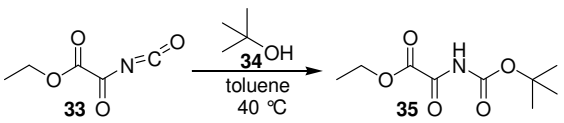
LBC-I-37 (785 mg, 11.36 mmol) and 10 ml anhydrous THF were added to a dry flask under argon. Triethylamine (3.17 ml, 22. 72 mmol) was added next followed by a slow addition of SES-Cl (1.96 g, 11.36 mmol). The reaction stirred for one hour and was then concentrated. The product was purified via a silica column using the following graduated solvent system: 20% ethyl acetate, 80% hexanes; 50% ethyl acetate, 50% hexanes; and 100% ethyl acetate. 129 mg was obtained as an oil, giving a 7% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.69 (s, 1H), 2.95 (m, 2H), 2.46 (t, *J* = 6.4 Hz, 2H), 2.19 (t, *J* = 2.3 Hz, 2H), 1.11 (m, 2H), 0.05 (s, 9H).

LBC-I-67



Ethyl oxamate (5.0 g, 42.70 mmol) was suspended in 15 ml anhydrous 1,2-dichloroethane at 0-degree Celsius. Oxalyl chloride (4.93 ml, 55.50 mmol) was added to this suspension. The reaction was warmed to reflux and then refluxed for 4 hours. The reflux condenser head was replaced by a distillation head. 1,2-dichloroethane was distilled off along with oxalyl chloride. The resulting mixture was cooled to room temperature and the residue was distilled under high-vacuum. 4.281 g was obtained as a clear oil, giving a 70% yield. The spectral data matched those in the literature.[2]

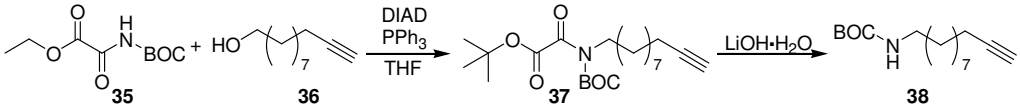
LBC-I-68



LBC-I-67 (4.281 g, 29.90 mmol) was dissolved in 40 ml anhydrous toluene. This

solution was placed in an ice water bath. Tert-butyl alcohol (3.23 ml, 34.4 mmol) was then added. The reaction stirred in the ice bath for 15 minutes. Afterwards, the reaction was warmed to room temperature and stirred for another 15 minutes. Then, the reaction was placed in a 40-degree Celsius oil bath and stirred for 30 minutes. The reaction was cooled to room temperature and stirred for 30 minutes. The final reaction mixture was concentrated into a clear oil. 6.135 g was obtained, giving a 95% yield. The spectral data matched those in the literature.[2]

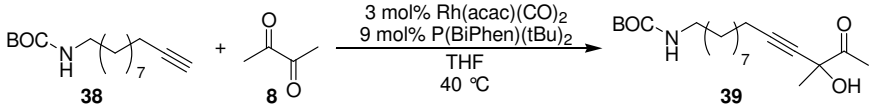
LBC-I-74



Triphenylphosphine (5.29 g, 20.17 mmol) was added to a flame-dried flask followed by 36 ml anhydrous THF. 10-undecyne-1-ol (5.32 ml, 27.60 mmol) and LBC-I-68 (4.0 g, 18.40 mmol) were added next. The reaction was placed in an ice water bath, after which diisopropyl-azo-dicarboxylate (3.97 ml, 20.17 mmol) was slowly added dropwise. The reaction was removed from the ice water bath, warmed to room temperature, and stirred overnight. The final reaction mixture was concentrated. The white precipitate was filtered off and washed with dichloromethane. Lithium monohydrate (727 mg, 17.31 mmol) was dissolved in 9 ml distilled water in a new, clean flask. 10 ml anhydrous THF was then added followed by the white precipitate (2.12 g, 5.77 mmol). The reaction stirred for 24 hours. More distilled water was added to the final reaction mixture. The organic layer was extracted two times with dichloromethane. The resulting organic extracts were combined, dried with sodium sulfate, and concentrated into a white solid. 1.88 g was obtained, giving a 73% yield. Melting point = 41.0-43.5

degrees Celsius. TLC R_f = 0.68 (30% ethyl acetate, 70% hexanes). IR (film): 2930.1, 2117.7, 1696.7. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.47 (s, 1H), 3.08 (q, *J* = 8.4, 6.6 Hz, 2H), 2.16 (t, *J* = 7.2 Hz, 2H), 1.92 (t, *J* = 2.7 Hz, 1H), 1.45 (s, 14H), 1.27 (s, 9H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 156.37, 85.12, 79.36, 68.47, 41.0, 30.45, 29.77, 29.60, 29.39, 29.08, 28.82, 27.15, 18.76. Anal calcd for $C_{16}H_{29}NO_2$: C, 71.86; H, 10.93; N, 5.24. Found: C, 71.60; H, 11.14; N, 5.27.

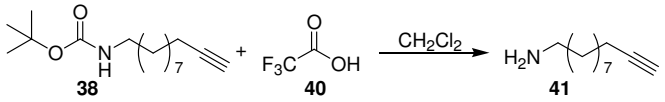
LBC-I-77



Dicarbonylacetylacetonato-rhodium (I) (2.89 mg, 0.0112 mmol) and 2-(di-t-butylphosphino)-biphenyl (10.03 mg, 0.0336 mmol) were added to a dry test tube under argon. 2,3-butanedione (289 mg, 3.36 mmol), LBC-I-74 (300 mg, 1.12 mmol), and 1.4 ml anhydrous THF were added to a second dry test tube under argon. The second test tube was degassed as its contents stirred at room temperature for ten minutes. After thorough stirring, the mixture in the second test tube was placed into the first test tube containing the rhodium and the ligand. The reaction was then placed in a 40-degree Celsius oil bath and stirred for 24 hours. The final reaction mixture was concentrated and the product was purified via a silica column using a solution of 40% ethyl acetate, 60% hexanes as the solvent system. 0.139 g was obtained as a yellow oil, giving a 35% yield. TLC R_f = 0.40 (30% ethyl acetate, 70% hexanes). IR (film): 3369.5, 2930.8, 2212.2, 1721.44, 1691.8. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.64 (s, 1H), 4.09 (s, 1H), 3.02 (q, *J* = 9.9, 6.3 Hz, 2H), 2.31 (s, 3H), 2.13 (t, *J* = 6.9 Hz, 2H), 1.51 (s, 3H), 1.40 (s,

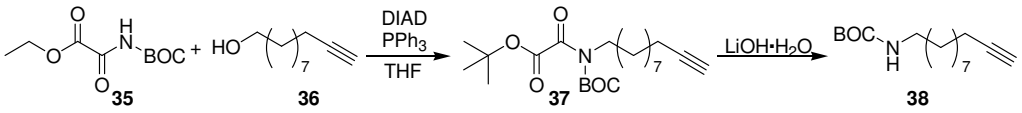
14H), 1.21 (s, 3H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 206.75, 156.38, 86.99, 79.92, 77.70, 72.89, 40.94, 30.40, 29.71, 29.54, 29.29, 29.13, 28.78, 27.09, 23.58, 19.23, 19.02. Anal calcd for $C_{20}H_{35}NO_4$: C, 67.95; H, 9.98; N, 3.96. Found: C, 64.49; H, 9.51; N, 3.93.

LBC-I-82



LBC-I-74 (300 mg, 1.12 mmol) was added to a flask followed by 2 ml dichloromethane. Trifluoroacetic anhydride (0.17 ml, 2.24 mmol) was added next. The reaction stirred for 1.25 hours at room temperature. A second addition of trifluoroacetic anhydride (0.08 ml, 1.12 mmol) was then added. The reaction stirred for another 3 hours. Excess acid was quenched with saturated sodium bicarbonate. The organic layer was extracted two times with dichloromethane and then washed with saturated sodium bicarbonate and brine. The organic extracts were dried with sodium sulfate and concentrated into a white solid. 138 mg was obtained, giving a 74% crude yield. The spectral data matched those in the literature.[6]

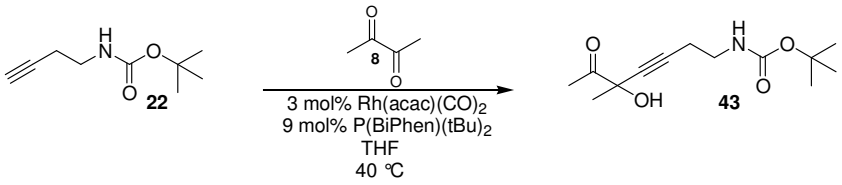
LBC-I-47



Triphenylphosphine (2.65 g, 10.09 mmol) was added to a flame-dried flask followed by 18 ml anhydrous THF. 3-butyne-1-ol (1.04 ml, 13.8 mmol) and LBC-I-68 (2.0 g, 9.20 mmol) were added next. The reaction was placed in an ice water bath, after which diisopropyl-azo-dicarboxylate (1.99 ml, 10.09 mmol) was

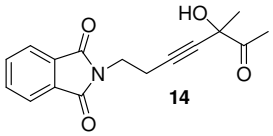
slowly added dropwise. The reaction was removed from the ice water bath and warmed to room temperature. It was then stirred overnight and concentrated. The white precipitate was vacuum-filtered off and washed with dichloromethane. The filtrate was concentrated and placed into a clean, dry flask. 35 ml of anhydrous THF was added next followed by lithium hydroxide (0.94 g, 39.27 mmol) dissolved in 28 ml distilled water. The reaction stirred for 3 hours at room temperature. 35 ml distilled water was added to the final reaction mixture. The organic layer was extracted two times with 70 ml dichloromethane. The organic extracts were combined, dried with sodium sulfate, and concentrated into an oil. 1.82 g was obtained, giving an 82% yield. TLC R_f = 0.56 (30% ethyl acetate, 70% hexanes). IR (film): 2978.4, 2120.1, 1699.3. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.92 (s, 1H), 3.18 (q, J = 7.5, 6.3 Hz, 2H), 2.29 (t, J = 6.9 Hz, 2H), 1.92 (t, J = 1.5 Hz, 1H), 1.35 (s, 9H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 156.07, 81.91, 79.30, 70.16, 39.57, 28.58, 20.09. Anal calcd for $C_9H_{15}NO_2$: C, 63.88; H, 8.93; N, 8.28. Found: C, 63.79; H, 8.93; N, 8.34.

LBC-I-53



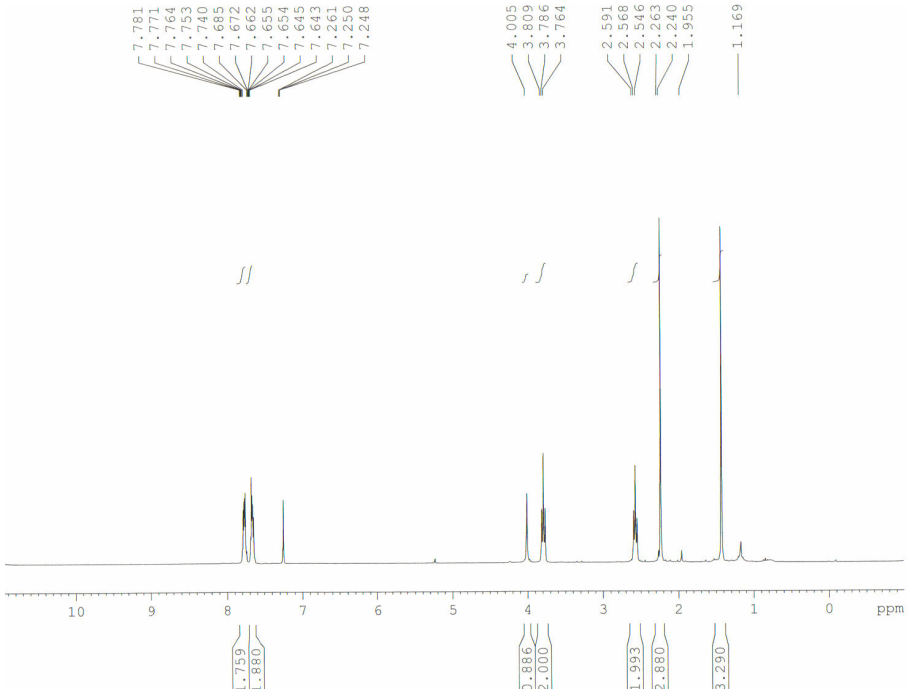
Dicarbonylacetylacetonato-rhodium (I) (4.64 mg, 0.02 mmol) and 2-(di-t-butylphosphino)-biphenyl (16.11 mg, 0.05 mmol) were added to a dry test tube under argon. 2,3-butanedione (259 mg, 3.0 mmol), LBC-I-47 (300 mg, 1.77 mmol), and 1.25 ml anhydrous THF were added to a second dry test tube under

argon. The second test tube was degassed as its contents stirred at room temperature for ten minutes. After thorough stirring, the mixture in the second test tube was placed into the first test tube containing the rhodium and the ligand. The reaction was then placed in a 40-degree Celsius oil bath and stirred for 24 hours. The final reaction mixture was concentrated and the product was purified via a silica column using a solution of 40% ethyl acetate, 60% hexanes as the solvent system. 0.437 g was obtained as an oil, giving a 97% yield. TLC R_f = 0.25 (30% ethyl acetate, 70% hexanes). IR (film): 3370.1, 2979.7, 2250.5, 1722.1, 1692.1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.80 (s, 1H), 4.09 (s, 1H), 3.24 (q, J = 3.9, 6.0 Hz, 2H), 2.39 (t, J = 2.1 Hz, 2H), 2.36 (s, 3H), 1.56 (s, 3H), 1.47 (s, 9H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 206.53, 156.19, 83.96, 81.36, 79.74, 72.86, 39.54, 28.69, 27.34, 23.64, 20.59. Anal calcd for $C_{13}H_{21}NO_4$: C, 61.16; H, 8.29; N, 5.49. Found: C, 58.58; H, 7.95; N, 5.42.

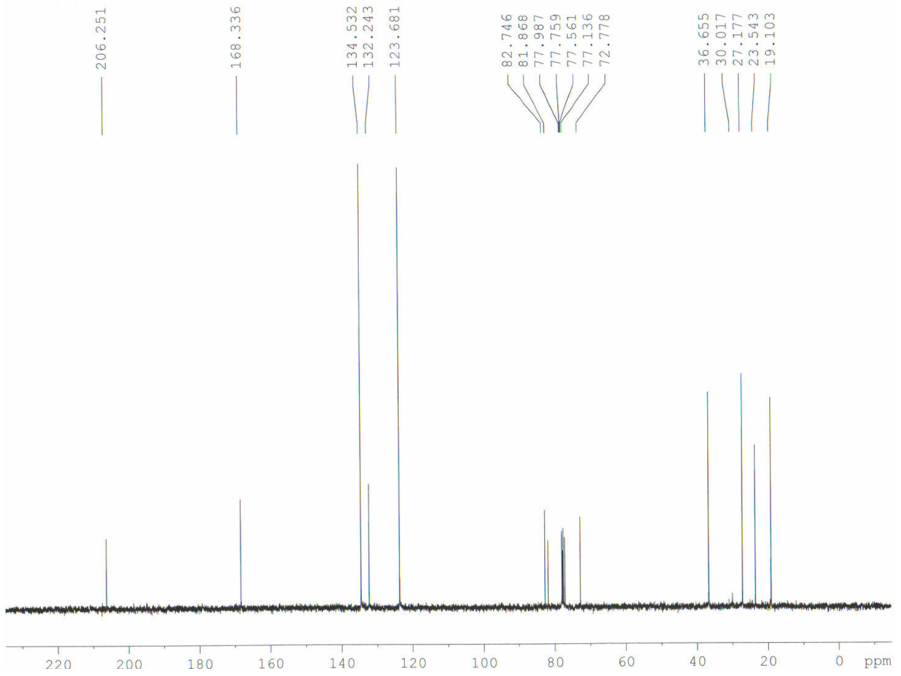


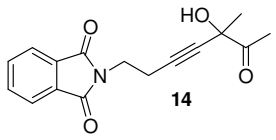
14

^{1}H NMR Spectrum



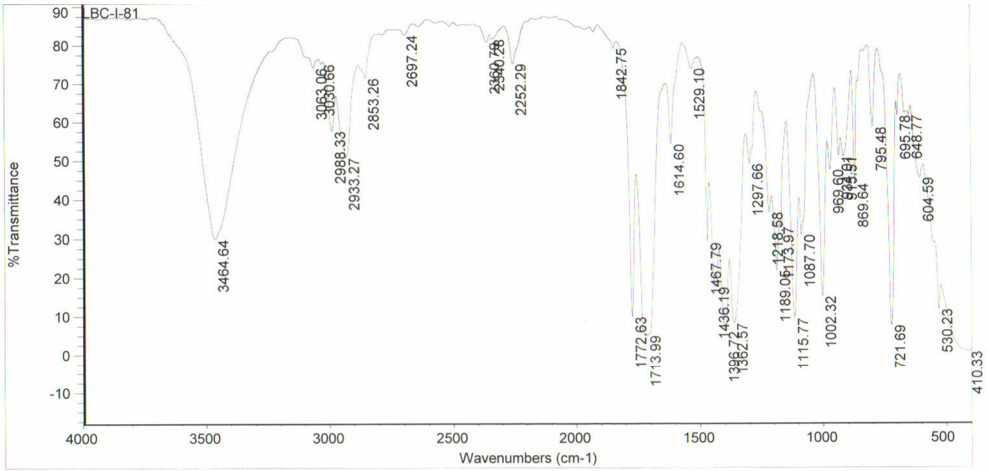
^{13}C NMR Spectrum

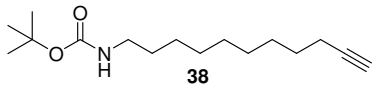




14

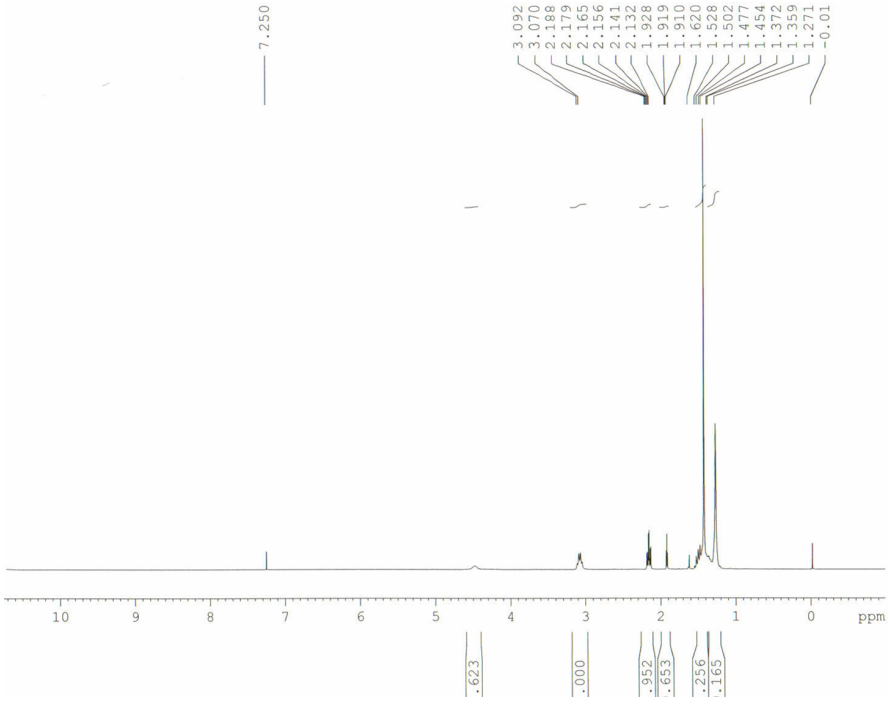
IR Spectrum



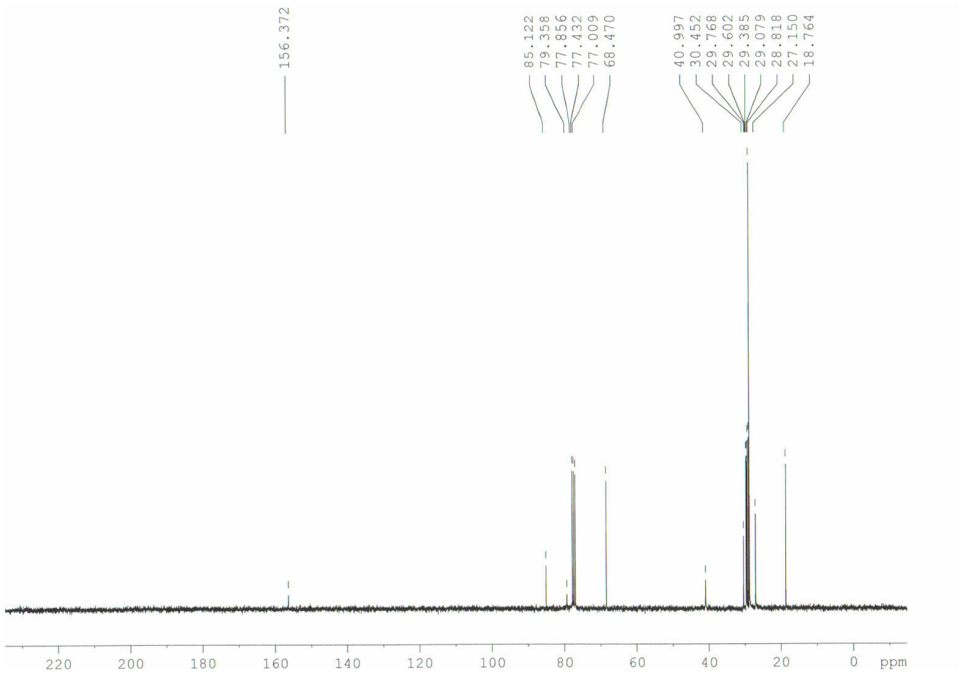


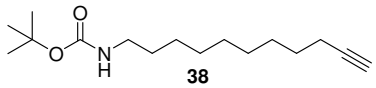
38

[1]H NMR Spectrum



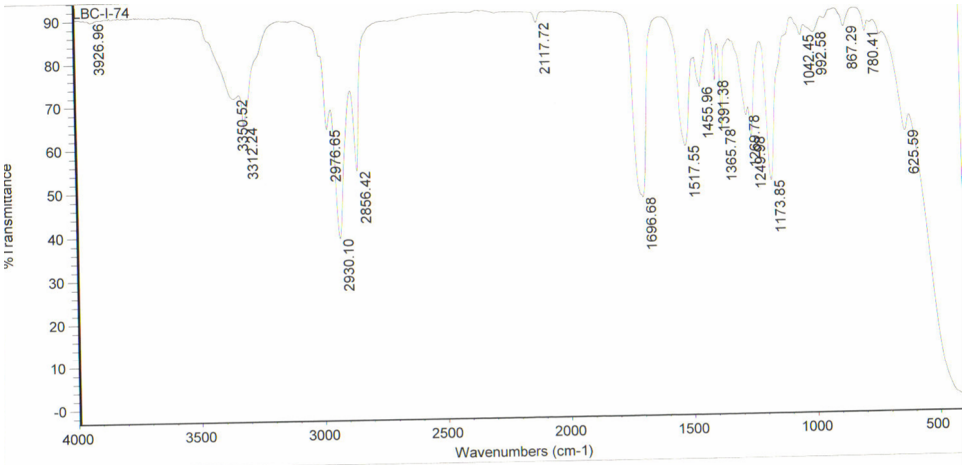
[13]C NMR Spectrum

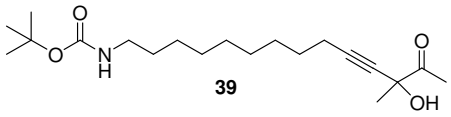




38

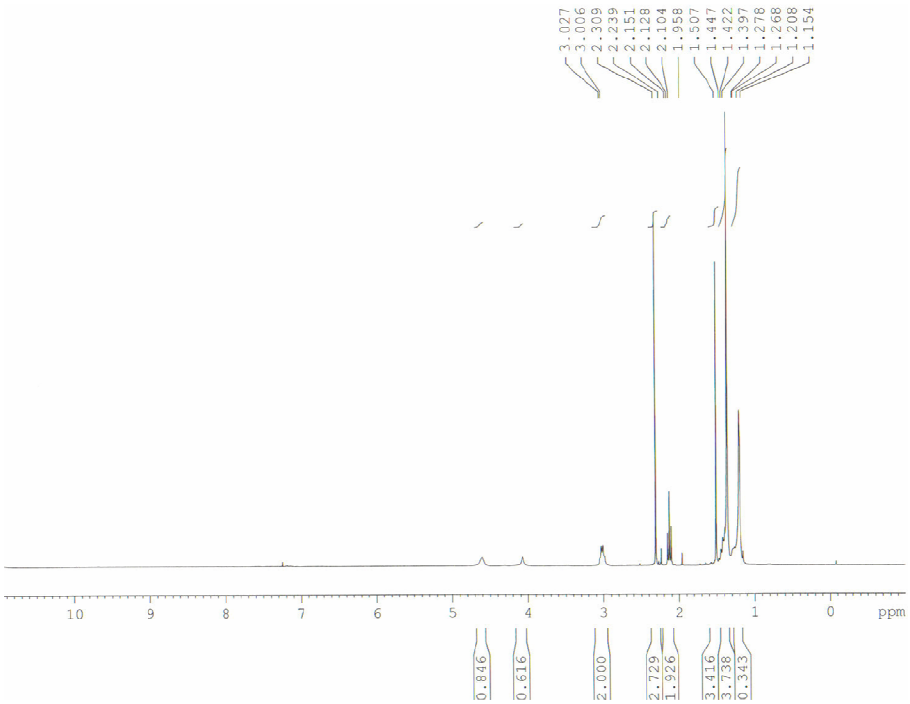
IR Spectrum



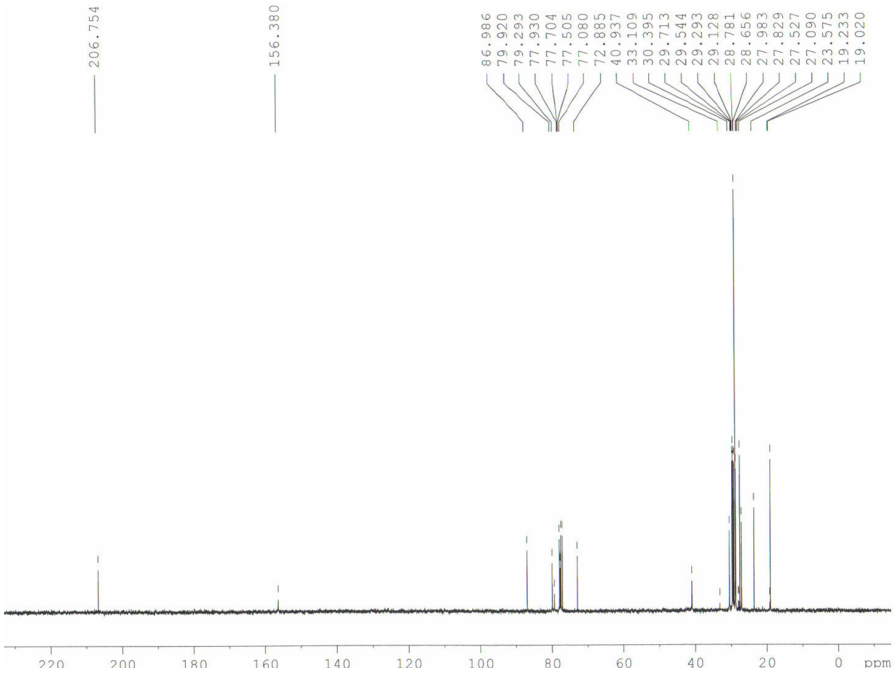


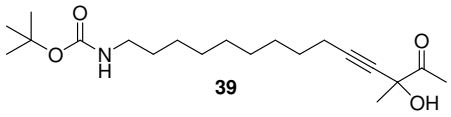
39

[1]H NMR Spectrum



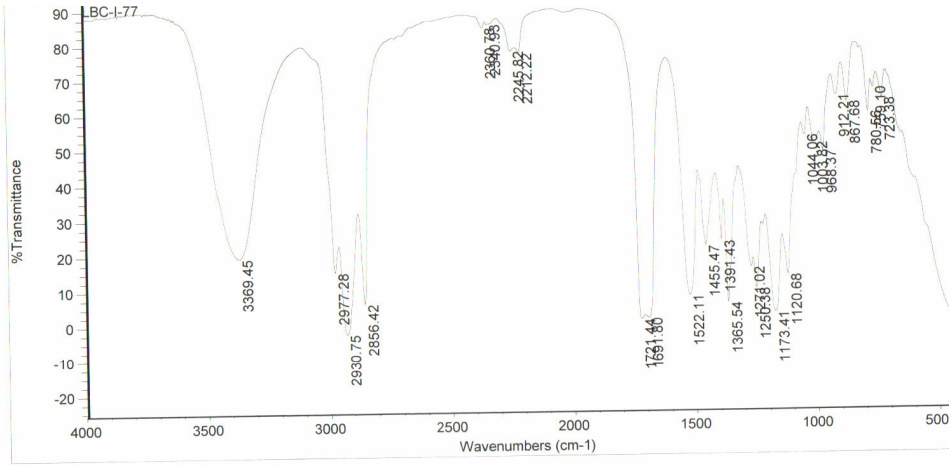
[13]C NMR Spectrum

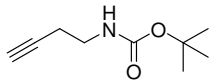




39

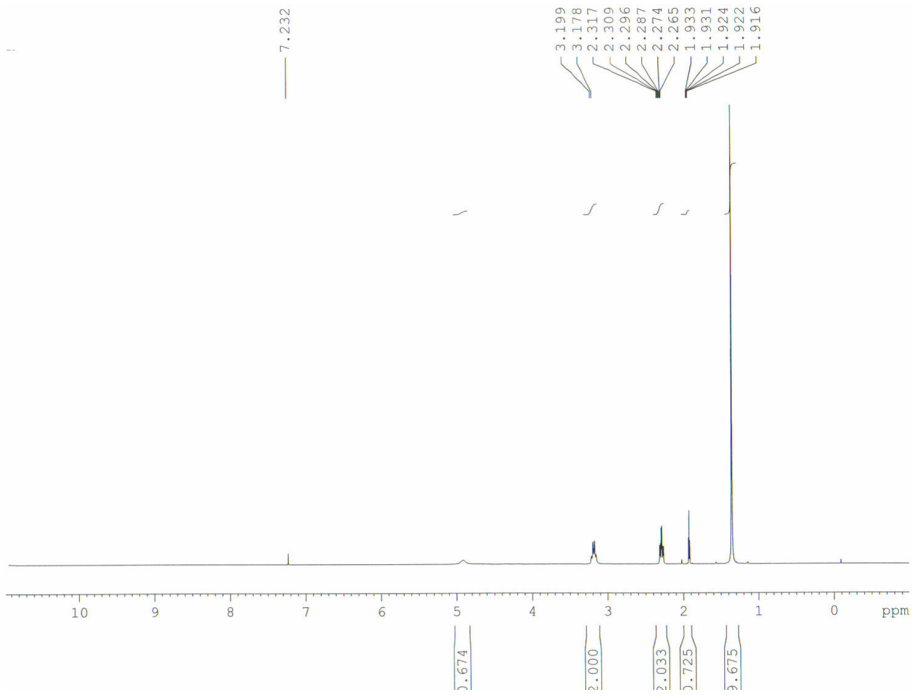
IR Spectrum



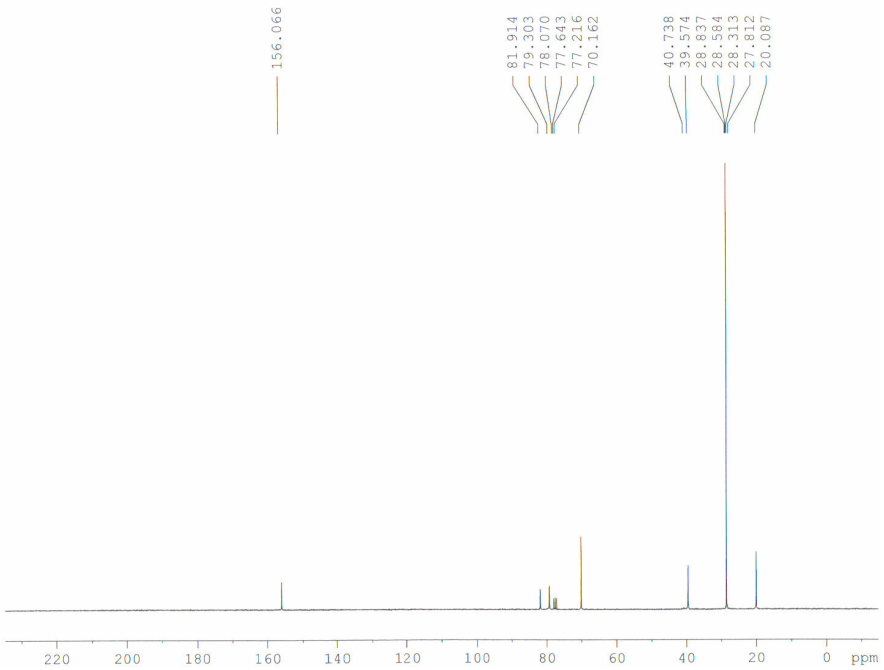


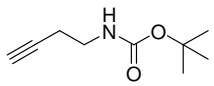
22

[1]H NMR Spectrum



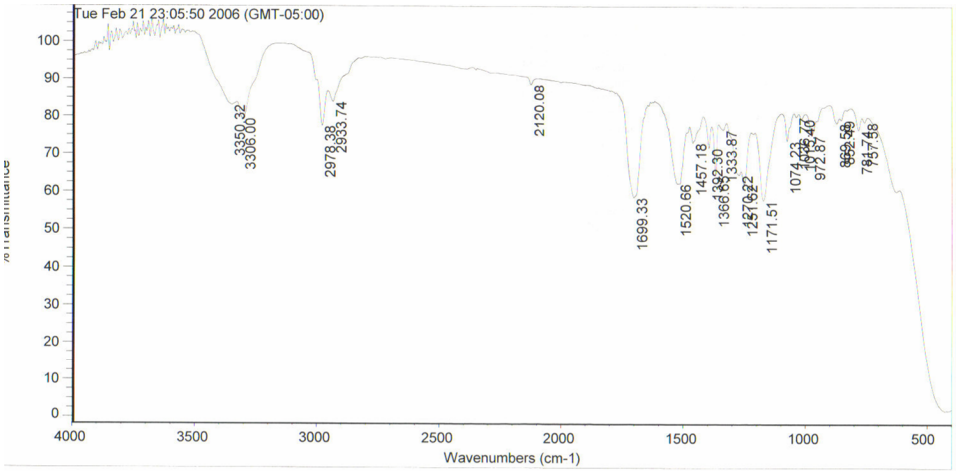
[13]C NMR Spectrum

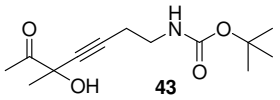




22

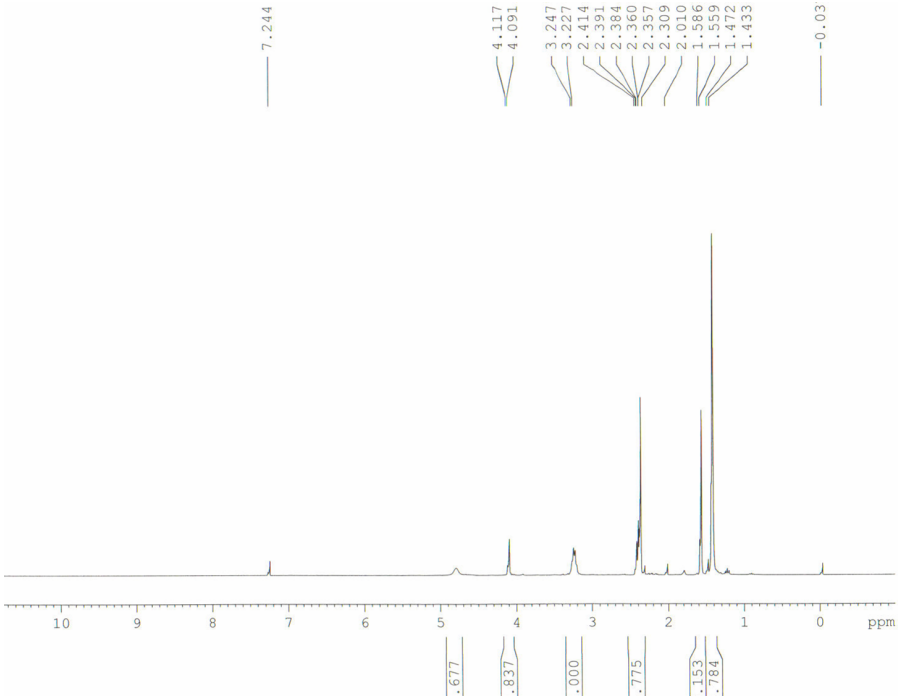
IR Spectrum



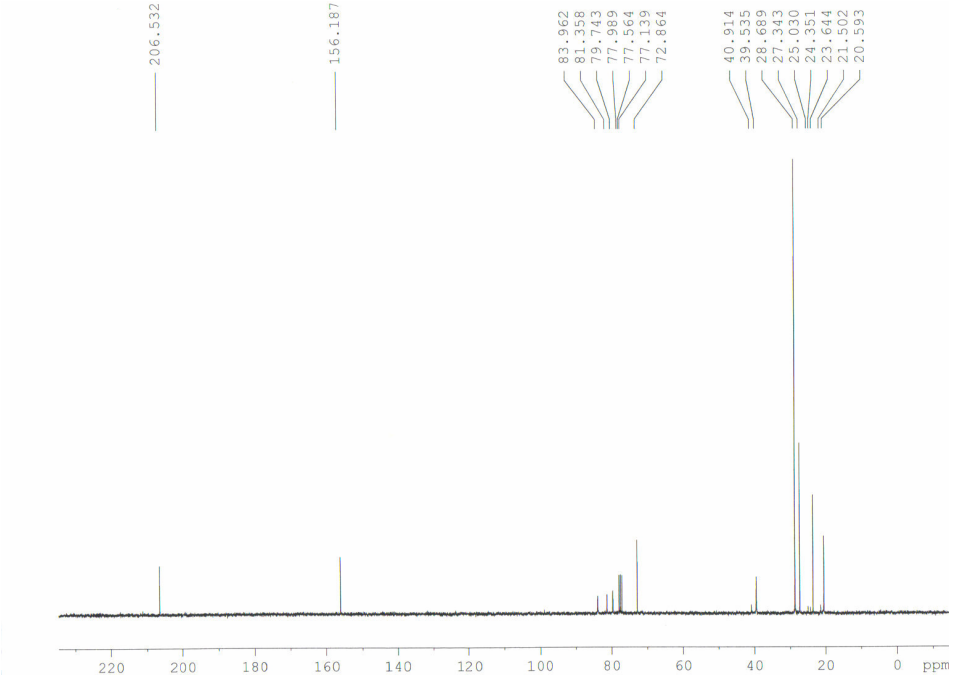


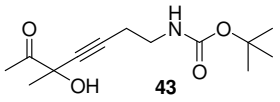
43

[1]H NMR Spectrum



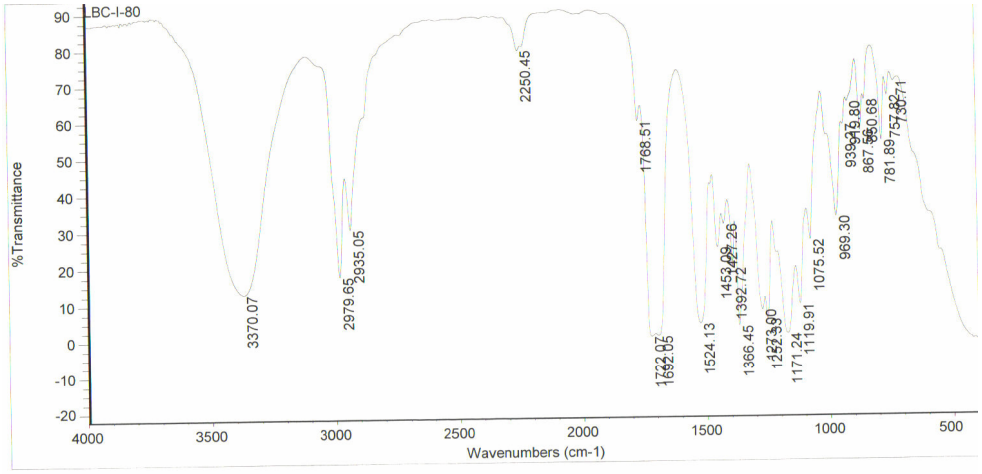
[13]C NMR Spectrum





43

IR Spectrum



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