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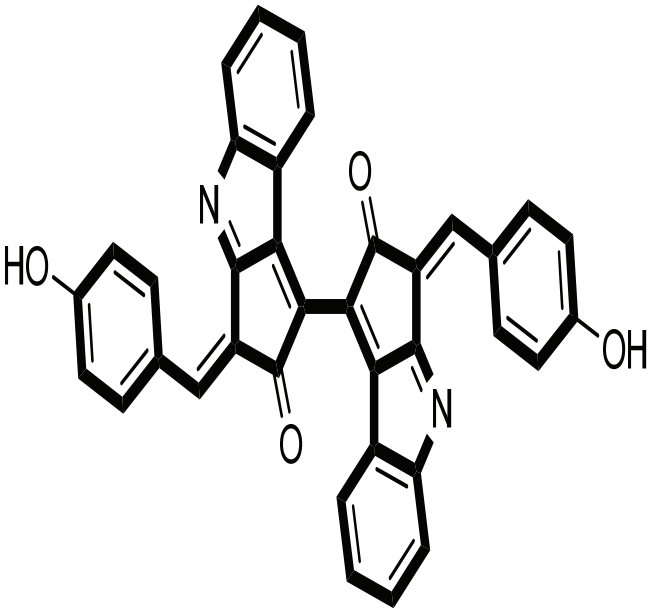

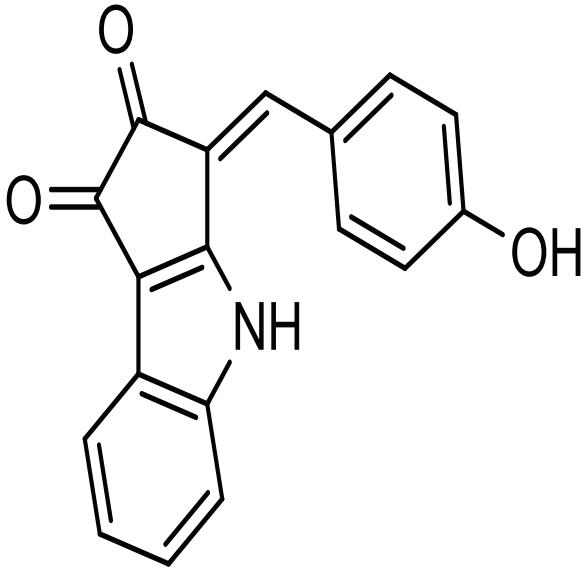

GOLD-CATALYZED INTRAMOLECULAR CARBOCYCLIZATION AND ISOMERIZATION OF INDOLES

Master of Science Thesis in Chemistry and Bioscience

LUCY IDOWU AJAKAIYE
Department of Chemical and Biological Engineering

Division of Organic Chemistry

CHALMERS UNIVERSITY OF TECHNOLOGY

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Supervisors: Professor Jerker Mårtensson
MSc Andreas Ekebergh
Examiner: Professor Nina Kann

Lucy Idowu Ajakaiye
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Lucy Idowu Ajakaiye

Department of Chemical and Biological Engineering
Chalmers University of Technology
SE-412 96 Göteborg
Sweden

Abstract

Scytonemin and nostodione A are cyanobacteria sunscreen pigments that have interesting biological properties. The ring structures of scytonemin and nostodione A are closely related and unique among natural products. The structure is proposed to stem from the condensation of tryptophan and tyrosine-derived subunits.

Gold-catalyzed cyclizations of aromatic and heteroaromatic compounds with alkynes offer new ways for the efficient construction of bioactive compounds, and have attracted much attention in the last decade.

Gold-catalyzed intramolecular carbocyclization was used with the intention of constructing cyclopenta[*b*]indol ring systems, present in scytonemin and nostodione A, from indoles with alkynes tethered to position three. Two bond tethers gave exclusively carbazoles and one bond tethers gave a rearrangement of the alkyne. Both type of systems were explored using different gold catalysts and solvents.

Keywords: Scytonemin, nostodione A, carbazoles, gold-catalyzed cyclization

Table of Contents

List of abbreviations

Bn ..... Benzyl

DCM ..... Dichloromethane

DMF ..... Dimethylformamide

Et_3N ..... Triethylamine

EtOH ..... Ethanol

Me ..... Methyl

NMP ..... *N*-Methylpyrrolidone

NMR ..... Nuclear magnetic resonance

THF ..... Tetrahydrofuran

TMS ..... Trimethylsilyl

OTf ..... Trifluoromethanesulfonate

1. Introduction

1.1 Background

Natural products and synthetic compounds containing the indole moiety possess an extraordinary range of important biological activities.[1-12] The indole unit can be found in many naturally occurring products such as Scytonemin, Nostodione A and Carbazoles, all which have interesting biological properties. They have further been used as substrates for number of useful chemical transformation. Cyanobacteria also known as blue-green algae, are a rich source of bioactive secondary metabolites with many potential applications.[13] The cyanobacteria sunscreen pigments scytonemin was first reported more than 150 years ago.[14] Scytonemin (Figure 1a) is a photostable dimeric alkaloid synthesized in numerous strains of cyanobacteria.[15] It is a lipophilic, yellow-brown pigment with a unique, highly conjugated heterocyclic skeleton.[16] The bacterial secondary metabolite is confirmed to have a role as a sunscreen; its biosynthetic gene cluster is triggered by exposure to UV light, which results in extracellular pigment accumulation and blockage of further incident radiation.[17, 18] The UV-absorbing ability of scytonemin is based on its highly conjugated chemical structure, [19] Scytonemin has a broad absorption from 325-425 nm and separate maximum at 250 nm.[16] Scytonemin was originally discovered in 1849 in some terrestrial cyanobacteria and later termed scytonemin. The structure remained unsolved until 1993, when Proteau et al. elucidated its chemical structure.[16] Scytonemin is believed to be the earliest developed substance that has the mechanism of UV protection, more ancient than the flavanoids or melanins.[20] Its ring structure, named the “scytoneman skeleton” stems from the condensation of tryptophan and tyrosine-derived subunits and is also closely related to the natural product nostodione A (Figure 1b).[16] Other attractive structural features include its lack of chirality, multiple dissection points and phenolic groups that could be easily modified.[21] Aside from its interesting photophysical properties, it has interesting biological properties such as kinase inhibiting, anti-flammatory and anti-proliferative properties, and has therefore been proposed as a pharmacophore used in the development of new therapeutically drugs.[22] Nostodione A (Figure 1b) was reported to be isolated from the cyanobacterial strain *Nostoc commune*.[23] It has also been previously obtained by ozonolysis of scytonemin.[16] Nostodione A is known to exist as two isomers in solution.[23] The UV spectrum of nostodione A shows absorption maxima at 280, 300, and

383 nm. Carbazole alkaloids (Figure 1d) are aromatic hetercyclic compounds isolated from the family of flowering plants known as *Rutaceae*-family.[24] They have many biological activities. In this study, synthesis of the common intermediate, the scytonemin monomer (Figure 1c) and nostodione A (Figure 1b) using Au-catalyzed cyclization will be the centre of attention.

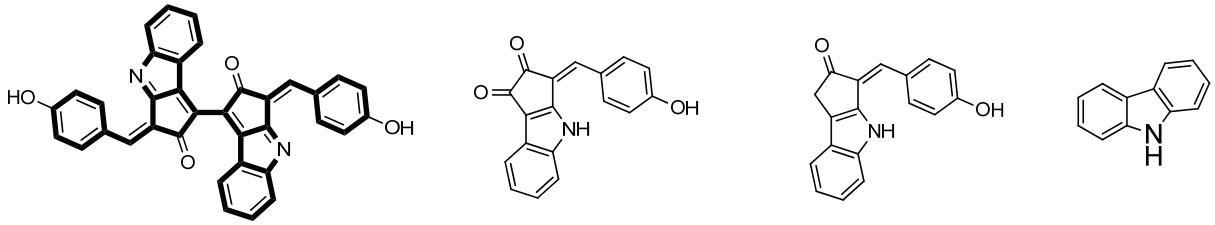


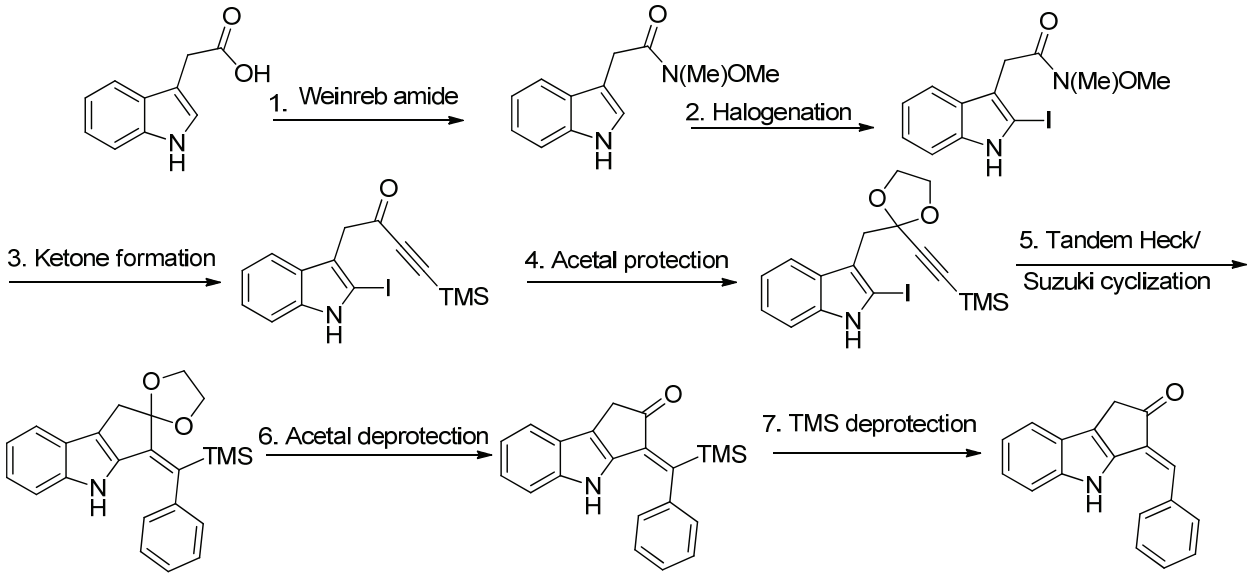
Figure 1. a) Scytonemin with the scytoneman skeleton in bold. b) Nostodione A. c) The scytonemin monomer. d) Carbazole alkaloid

Gold-catalyzed cyclizations of aromatic and heteroaromatic compounds with alkynes offer new ways for the efficient construction of bioactive compounds, and have attracted much attention in the last decade.[25] There is a great deal of attention drawn towards gold with respect to its chemical properties. Gold ions are known to activate carbon-carbon multiple bonds, especially alkynes, toward nucleophilic addition. Gold´s characteristic alkynophilicity and a variety of organic transformations catalyzed by gold have been investigated.[26-31] Gold is particularly attractive as it not only can conveniently be employed under experimentally simple open flask reaction conditions but also shows an outstanding functional group tolerance.[25] Gold ions also have anti-inflammatory properties and are used as pharmaceuticals in the treatment of arthritis and tuberculosis.[32-34] This first objective of this project was aimed at exploring the gold catalyzed reaction in reducing the initial 7 reaction steps to 3 (Scheme 1.2) making the synthesis of scytonemin monomer with analogues more efficient. The second objective was to synthesis nostodione A exploring Au-catalysed cyclization (Scheme 1.3). The substrate required for the gold catalyzed reaction is synthesized through a two-step sequence (Scheme 1.2, reaction 1 and 2) by already established methods. A set of scytonemin monomer derivatives has recently been

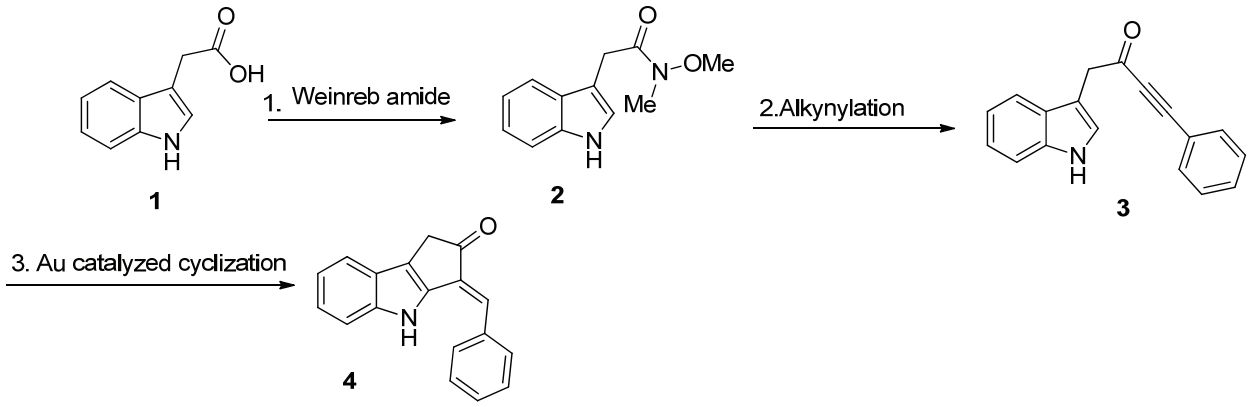
synthesized in our laboratory via a seven step sequence (Scheme 1.1). In this project, the quite new and fast growing field of gold catalysis is explored as a mean to reduce the current synthetic pathway by four transformations, thus constituting a synthetic ´´shortcut`` to scytonemin monomer. Gold catalysis was also explored as key method in the synthesis nostodione A.

1.2 Aim

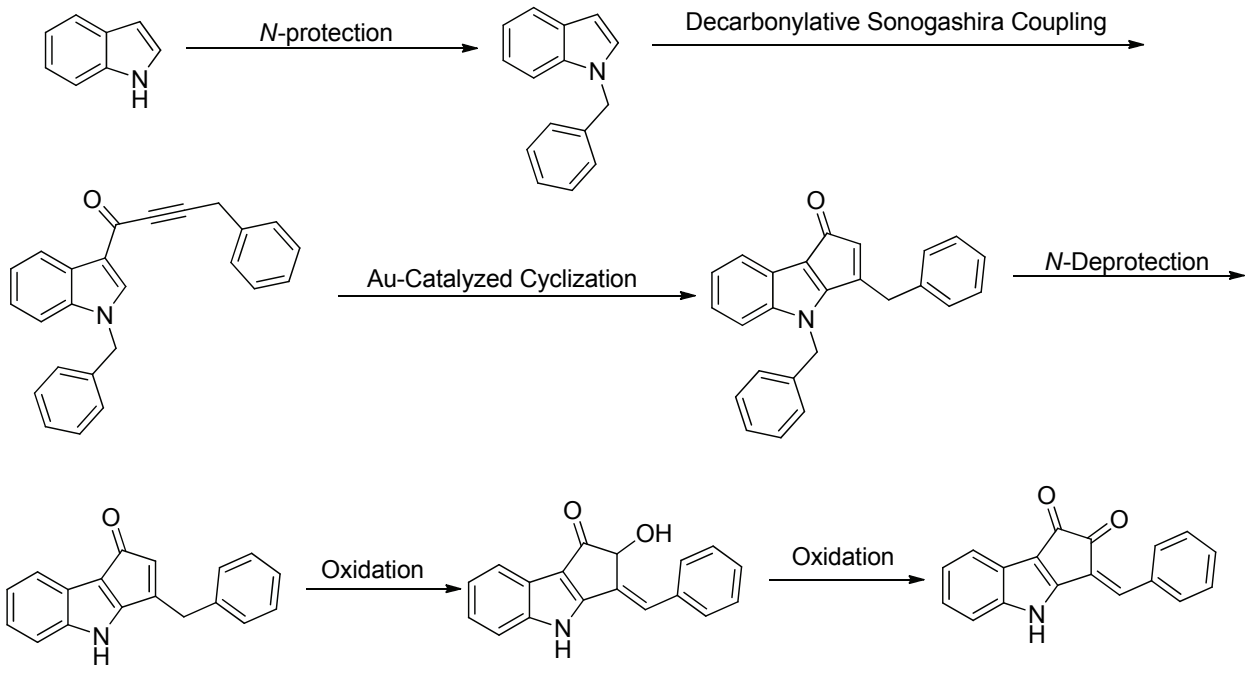
The aim of this project is to explore a possible synthetic shortcut to the scytonemin monomer using a gold catalyzed cyclization reaction. At present the only synthetic route to the scytonemin monomer (figure 1**c)**, developed locally at Chalmers by Ekebergh [36], has 7 reaction steps. Exploring Au catalyzed cyclization, will reduce the 7 reaction steps of the current stage of development of the synthetic route to the scytonemin monomer (Scheme 1.1) to 3 reaction steps (Scheme 1.2). The gold catalyzed reaction procedure will be optimized by varying several parameters. If successful, this will result in reduced number of reaction steps, and reduce the use of solvents, reagents, catalysts etc. compared to the current synthetic route of scytonemin. The result will be a more environmentally and economically benign method for preparing scytonemin with derivatives. Its purpose is also to contribute to the rather new field of gold catalysis.



Scheme 1.1 Current stage of development of the synthetic route to Scytonemin



Scheme 1.2 Synthetic route using Au catalyzed cyclization to Scytonemin



Scheme 1.3 Proposed Synthetic route using Au catalyzed cyclization to Nostodione A

2. THEORY

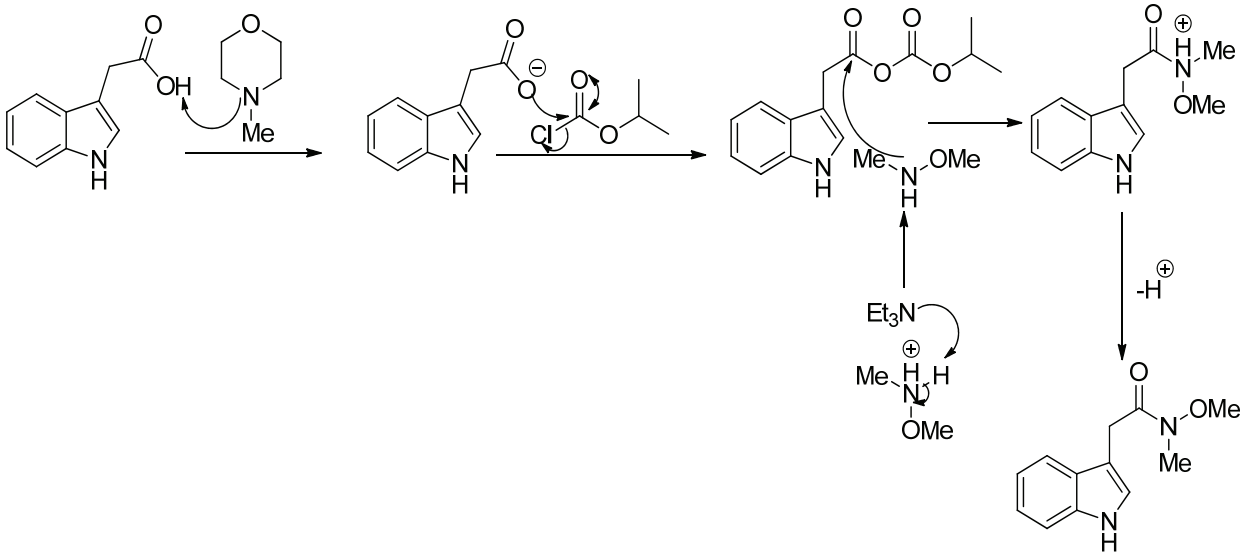
A theoretical background to the reactions involved in the two projects about gold-catalyzed intramolecular carbocyclization and isomerization of indoles is discussed in this chapter. It includes theories for Weinreb amide formation, alkynylation, gold-catalyzed cyclization, indole N-protection, decarbonylative Sonogashira coupling and gold-catalyzed isomerization.

2.1 Weinreb amide formation

Various methods of synthesizing ketones from carboxylic acid using organometallics have been carried out for decades. A major difficulty associated with this method is the reactivity of organometallic reagents and the tendency to overadd to the substrate, leading to the production of tertiary alcohol.[35] One method to overcome this problem is the formation of a Weinreb amide previous to the organometallic addition. Previous studies carried out at Chalmers [36, 37] have successfully used the Weinreb amide procedure in gram scale.

The Weinreb amide synthesis takes its start in the formation of an anhydride from the carboxylic acid by treating it with *N*-methylmorpholine and isopropyl chloroformate. Firstly, carboxylic acid is deprotonated by *N*-methylmorpholine followed by a nucleophilic attack on chloroformate. Low temperature of -20^{o}C is required because of the reactivity of chloroformate which is also sensitive to hydrolysis. Water must be excluded from the reaction as much as possible using dry solvents and dry apparatus under inert environment.

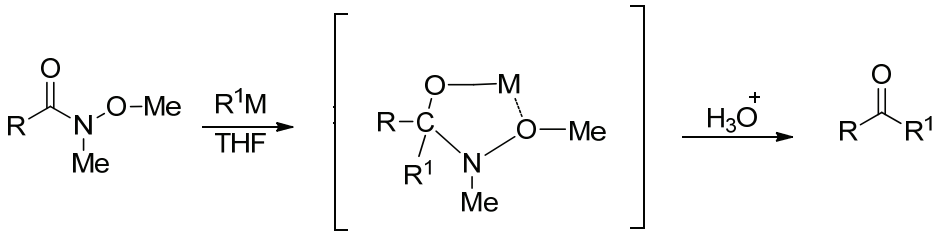
In the second part of the Weinreb amide synthesis, Et_3N deprotonates the hydrochloric acid salt of *N,O*-dimethylhydroxylamine. The anhydride acts as an electrophilic and undergoes a nucleophilic attack by *N,O*-dimethylhydroxylamine, followed by the removal of hydrogen from the nitrogen to give 2-(1H-Indole-3-yl)-N-methoxy-N-methylacetamide. This is illustrated in the reaction mechanism of Weinreb amide formation of carboxylic acid using isopropyl chloroformate as shown in **scheme 2.1.1** below.



Scheme 2.1.1 Reaction mechanism of Weinreb amide formation

2.2 Alkynylation

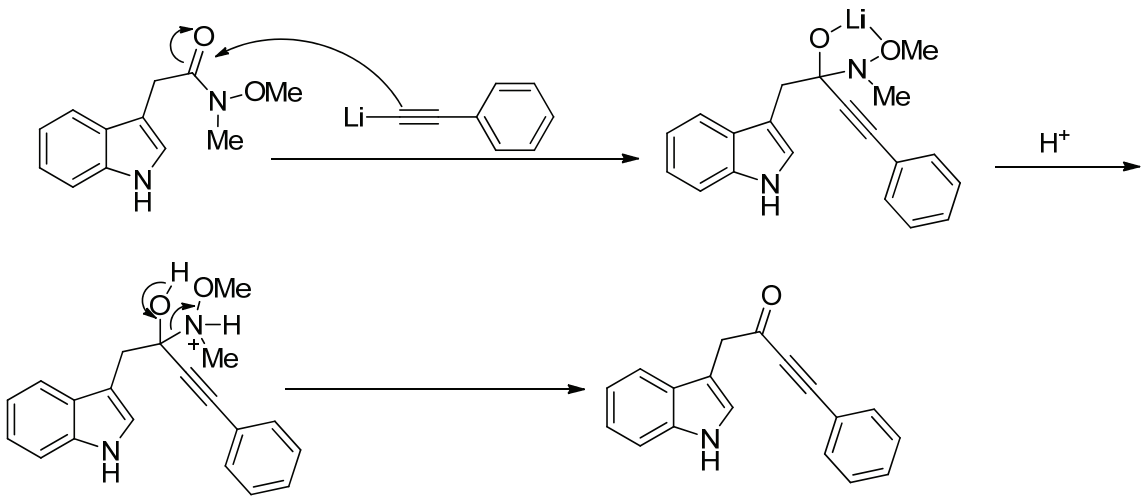
Previous studies of synthesizing ketones from carboxylic acids using Weinreb amide has shown that *N*-methoxy-*N*-methylacetamide gives a clean reaction with Grignard reagents and organolithium species in THF to form ketones. It has also been shown that it does not produce tertiary alcohol even when excess of organometallics are used. This clean reaction proceeds via a stable chelated intermediate as shown in **scheme 2.2.1**.[35]



Scheme 2.2.1 Synthesis of ketone from Weinreb amide in THF.

The alkynyl lithium reagent is formed in situ by treating the acetylene derivative with butyl lithium. Treating the Weinreb amide with the lithium reagent will result in a nucleophilic attack producing a stable tetrahedral intermediate by chelation of the lithium ion. The

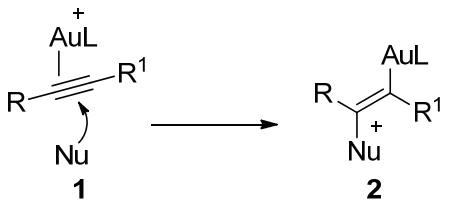
intermediate collapses upon treatment with an acid, forming the desired ketone. This is illustrated in **scheme 2.2.2**.



Scheme 2.2.2 Reaction mechanism for alkynylation.

2.3 Gold-catalyzed cyclization

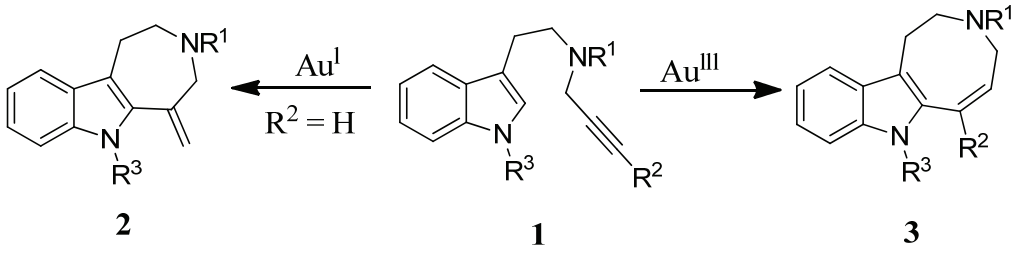
In the past years, studies have shown gold salts and their complexes to be powerful catalysts in the electrophilic activation of alkynes toward varieties of nucleophiles under homogenous conditions. Most reactions developed with homogeneous Au catalysts have exploited the propensity of Au to activate carbon-carbon π-bonds as electrophiles.[38, 39] In a simple form, the gold complex makes the alkyne very electrophilic leading to a nucleophilic attack by the nucleophile as illustrated in **scheme 2.3.1**.[38]



Scheme 2.3.1 Nucleophilic attack by a nucleophile

Compound **2** is the intermediate of Au catalyzed reactions. This type of co-ordination is common in gold-catalyzed cycloisomerizations of alkynes, where the alkene functionality acts as the nucleophile.[38]

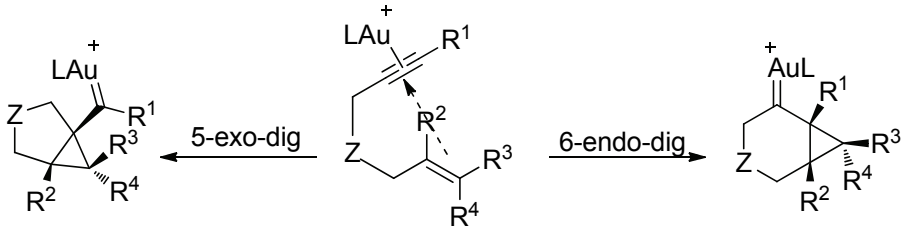
Previous study on gold catalyzed intramolecular reaction of indoles with alkynes have been done by Catalina Ferrer and Antonio Echavarren.[40] In their study both gold (I) and (III) complexes were used to control the selectivity on bigger rings (7-exo-dig and 8-endo-dig). This is shown in **scheme 2.3.2**



Scheme 2.3.2. 7-exo-dig versus 8-endo-dig cyclization of alkynyl indoles **1**.

2.3.1 Carbocyclization

Previous studies of cycloisomerization of enynes catalyzed by gold done by Núñez and co-workers, shows that gold coordinates with alkyne forming a complex. The resulting complex reacts with the alkene by either the 5-exo-dig or 6-endo-dig pathway to form the *exo*- or *endo*cyclopropyl gold carbene.[38] This is illustrated by **scheme 2.3.3.**

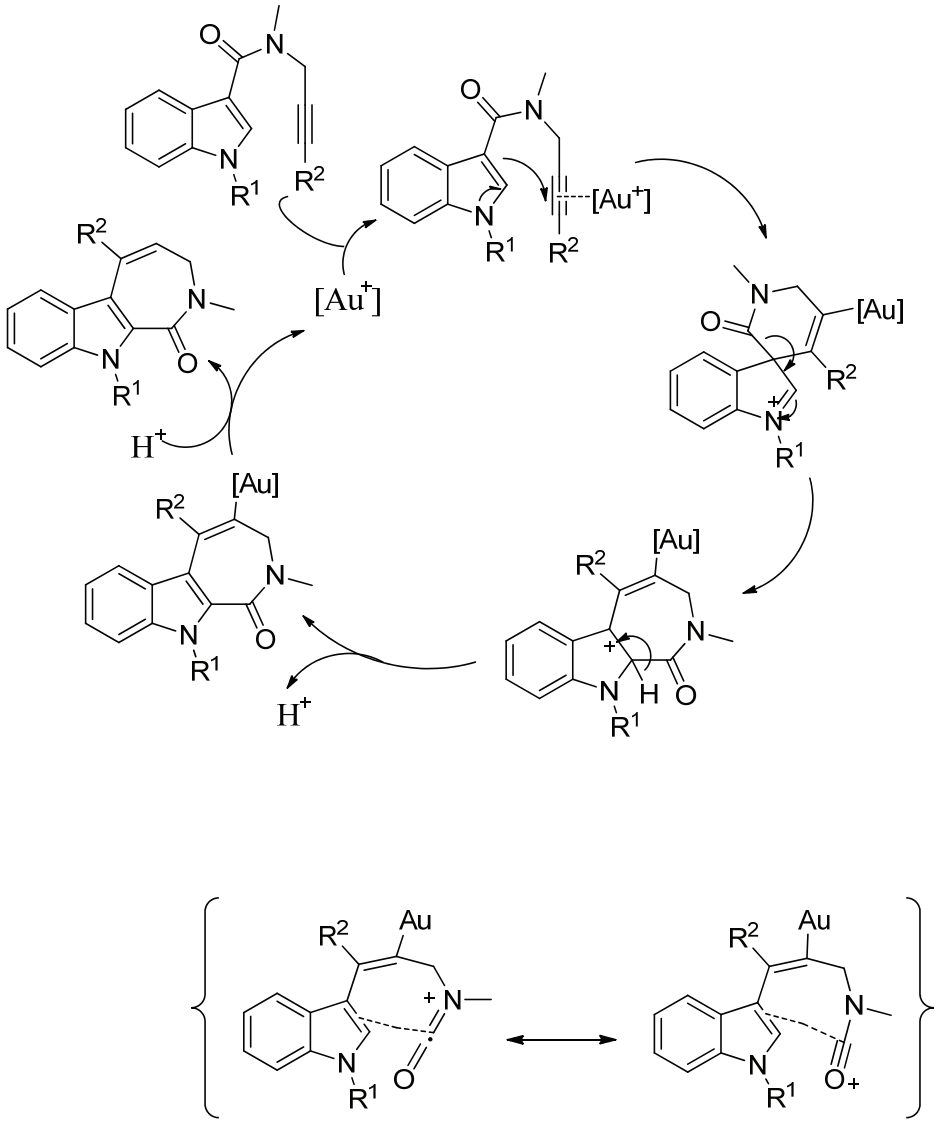


Scheme 2.3.3. Gold catalyzed cycloisomerization reported by Núñez and co-workers.

2.3.2 Wagner-Meerwein rearrangement (3, 2-shifts)

Gold catalysts act as π-acids and are capable of activating π-systems and then inducing rearrangements. With respect to selectivity and activity, the gold catalysts are often superior to related metals like platinum.[41] Wagner-Meerwein rearrangement is one of the reaction type observed in heterocyclic systems which involves arenium intermediates that rearomatize by rearrangement. This involves a shift of one of the substituents from the 3-position to the 2-position of the heterocyclic system and subsequent loss of a proton. [42] Wagner-Meerwein

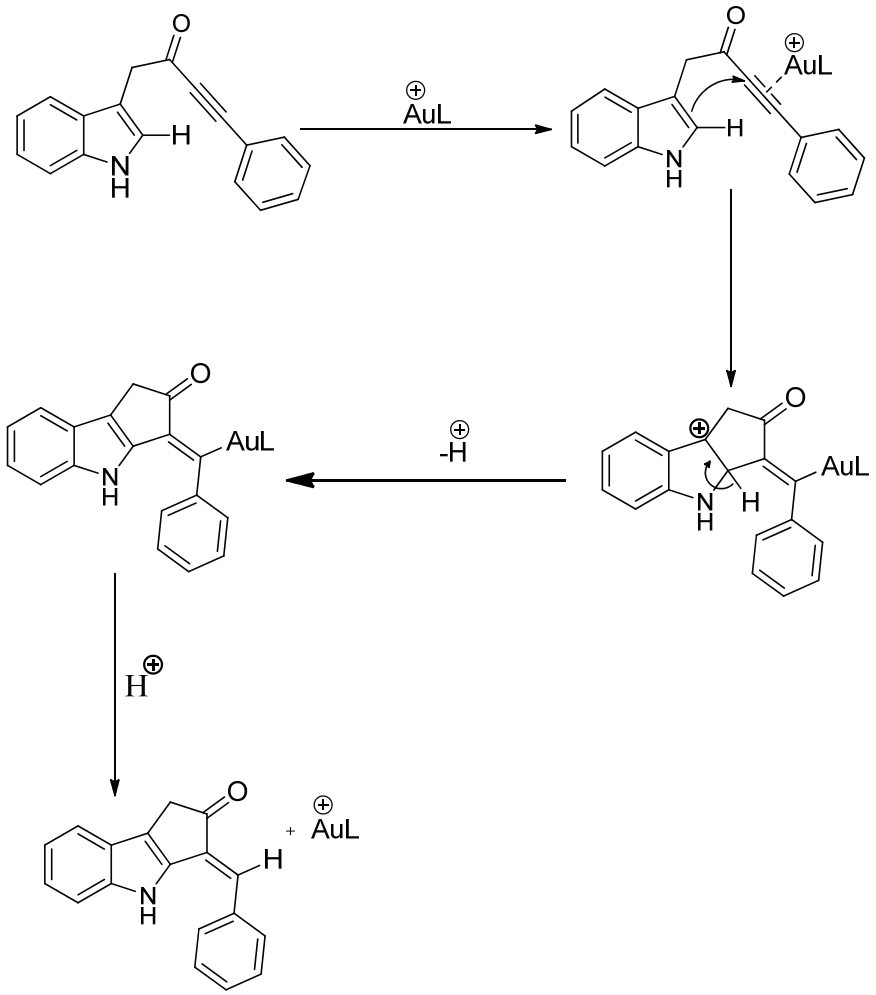
rearrangement (3, 2-shifts) has been observed in indole systems. [43] Previous study carried out by Hashmi and co-workers -shows the 3, 2-acylamino shift in indoles as illustrated in **scheme 2.3.4**.



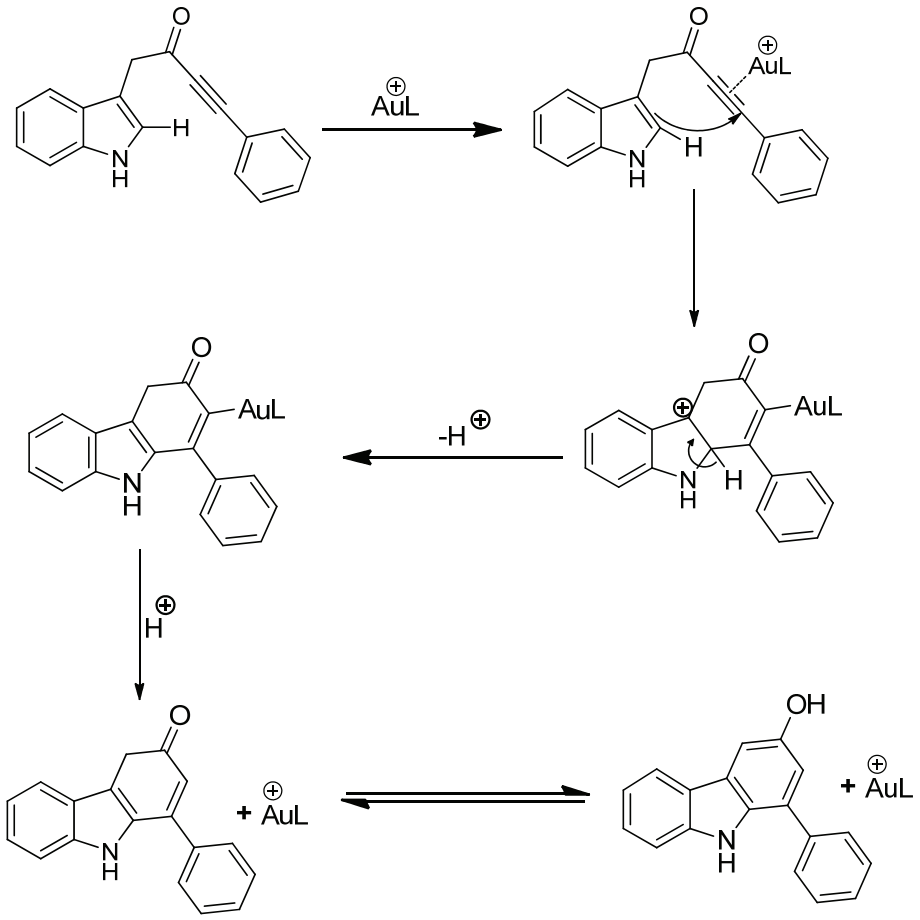
Scheme 2.3.4. Mechanistic proposal for 3,2-acylamino shift in indoles by Hashmi and co-workers.

Au catalyzed cyclization of the scytonemin precursor requires formation of a 5-membered ring. One major challenge associated with the cyclization is to bias the reaction in the direction of the desired product of correct ring size. The similarity in the energy for five membered and six membered rings can serve as a problem in obtaining the right compounds,

since the reaction will favour the thermodynamically most stable product. A proposed mechanism of Au catalyzed cyclization of scytonemin is illustrated in **scheme 2.3.5.**



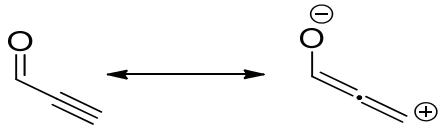
Scheme 2.3.5.1 Proposed mechanism of Au catalyzed cyclization for 5-exo-dig pathway



Scheme 2.3.5.2 Proposed mechanism of Au catalyzed cyclization for 6-endo-dig pathway.

2.3.3 Electronic effect

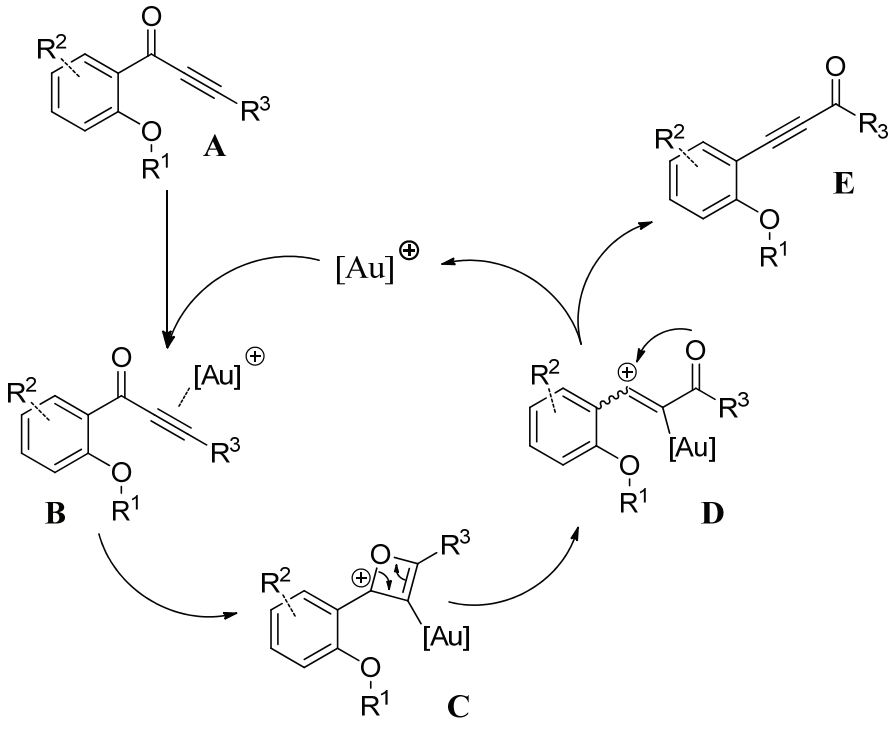
A carbonyl is a strong electron withdrawing group that is expected to have strong electronic effects on the Au catalyzed reaction. Electronic effect caused by the ketone will pull electrons from one of the two carbons of the alkyne. This will aid a nucleophilic attack on this electron poor carbon forming the 6-endo-dig product. Two ways of reducing the electronic effect are by either reducing the ketone to an alcohol or by acetal formation thereby protecting the ketone. These two ways were exploited in this project with the aim of driving the alkene to make a nucleophilic attack on the desired carbon of the two possible ones of the alkyne. The two ways may help drive the reaction to a 5-exo-dig product or at least a mixture of 5-exo-dig and 6-endo-dig products, respectively.



Scheme 2.3.6 Electronic effect of electron-drawing ketone.

2.3.4 Gold-catalyzed isomerisation

Using gold catalysis on substrates with α,β-unsaturated alkynes can give an isomeric ketone of the starting material. This isomerization reaction is likely to be related to the Meyer-Schuster rearrangement.[44] Previous study on electrophilic transfer of carbon in gold catalysis in the synthesis of chromosomes carried out by Renault and co-workers in 2011, has shown the possibility of giving an isomeric ketone of the starting material using gold catalysts. This is illustrated in **scheme 2.3.7.**



Scheme 2.3.7. Proposed catalytic cycle for gold-catalyzed isomerization by Renault and co-workers.

2.4 Reduction to alcohol and acetal formation

An attempt to reduce the electronic effect of ketone in this reaction was carried out in two ways. The first way was by reducing the ketone to an alcohol. The second way was by protecting the ketone (acetal formation).These two methods can be viewed in any classical organic textbook.[45,46]

2.5 *N*-Protection of indole

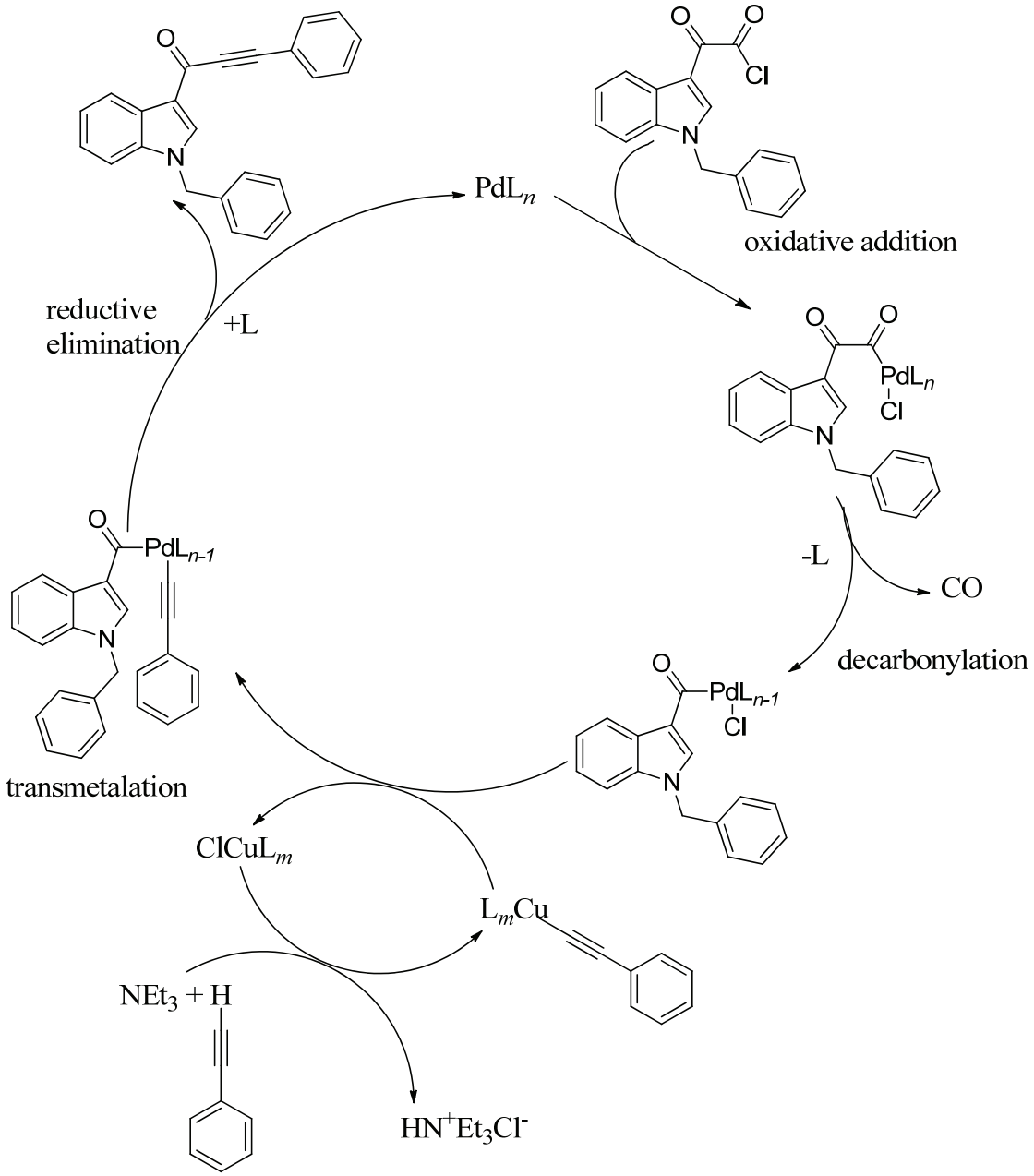
Synthetic compounds containing the indole moiety have been used as substrates for a number of useful chemical transformation. *N*-protecting groups and different substitutions at different positions of the indole ring are carried out to give excellent yields depending on the reaction.[47] Indole *N*-protection was carried out on the indole via a nucleophilic attack on benzyl bromide. This reaction step was done before decarbonylative Sonogashira coupling.

2.6 Decarbonylative Sonogashira Coupling

Alkynones are important intermediates in organic syntheses due to their bifunctional electrophilicity.[48-52] Decarbonylation of α-dicarbonyl compound has been carried out with different metal complexes such Rhodium-mediated decarbonylations of aldehydes (Tsuji–Wilkinson reaction) at temperature of 200^{o}C[53], Iridium-catalyzed decarbonylative homologizations of aroyl chlorides in boiling xylene were reported in 2002.[54,55] Palladium complexes are not commonly used for decarbonylations. Gooßen and Paetzold reported decarbonylative Heck reactions with reaction times of 16 h at 160 ^{o}C in NMP as a solvent.[56] Gooßen and co-workers in 2008 reported Pd/Cu-catalyzed decarboxylative cross-couplings of α-oxocarboxylates with aromatic bromides and chlorides[57] at high temperatures and long reaction times.

Merkul and co-workers in 2009 reported the first findings on consecutive three-component synthesis of alkynones by decarbonylative Sonogashira coupling starting from electron-rich heterocycles and oxalyl chloride as a source of the CO building block via intermediary glyoxylyl chlorides.[58] Many indole derivatives directly and without Lewis acid activation react with oxalyl chloride in a Friedel–Crafts acylation to furnish indole-3-glyoxylyl chlorides in high yields.[59] The indole-3- glyoxylyl chlorides obtained were reactive and unstable, and used as

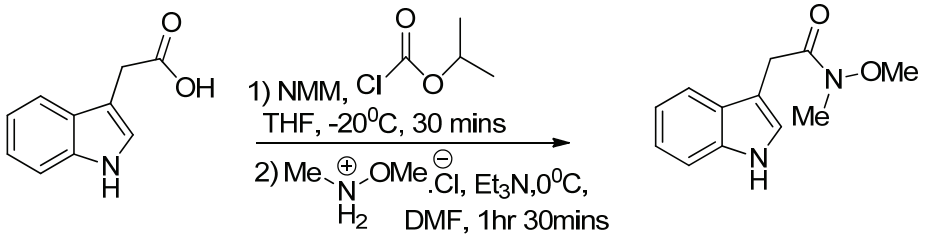
synthetic equivalents of acid chlorides in Palladium catalyzed cross-coupling reactions, establishing a decarbonylative alkynylation.[60] This is illustrated in **scheme 2.6.1.**



Scheme 2.6.1 Mechanistic rationale of the decarbonylative Sonogashira coupling of indole-3-glyoxylyl chlorides and alkyne.

3. Results and Discussion

3.1 Weinreb amide formation

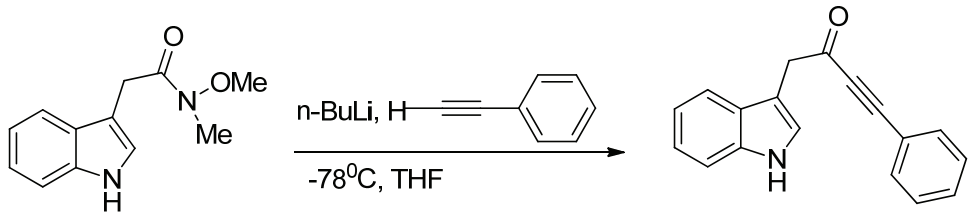


Scheme 3.1.1. Reaction conditions for the transformation of indol-3-acetic acid into the corresponding Weinreb amide.

Previous studies done locally at Chalmers by Ekebergh and Arshad[36,37] have been reported to give reproducible results in scales up to three grams of indol-3-acetic acid, giving yields of 80% and 75% respectively. This time the reaction was carried out on a ten grams scale and gave a yield of 70%. There are some factors responsible for this slightly lower yield.

The first factor was the poor solubility of *N,O*-dimethylhydroxylamine hydrochloride in DMF. This reagent remains as an undissolved white salt after quenching. Having unreacted reagents at the end of the reaction will of course result in a lower yield, but it can also enhance competing side reactions giving more by-products. This will lead to a more complex purification process, which also affects the yield.

3.2 Alkynylation



Scheme 3.2.1. The reaction conditions for alkylation.

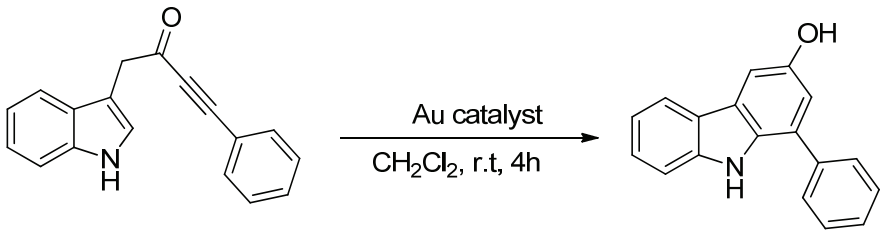
It has been shown that *N*-methoxy-*N*-methylacetamide gives a clean reaction with organolithium species in THF forming ketones. The alkynylation was carried out twice. The

first reaction gave a yield of 71%. However, the purification had to be done twice which could have affected the yield in an unfavorable way. The first purification process gave a yield of 96% but still had some impurities in the product which could be seen from the TLC. A second purification had to be done which gave the final yield of 71%. The second alkynylation gave a yield of 80%.

3.3 Au catalyzed cyclization

Studies have been done on the differences in reactivity and selectivity depending on the gold oxidation state and on the nature of the ligand used in the homogeneous catalyc reactions. The choice of Au catalysts can result in substantial variations in yields or efficiencies. The ligand, counterion, or oxidation state of Au enables control over the reaction pathways, e.g it may influences the diastereoselectivity, regioselectivity, and chemoselectivity of the reaction.[12] For Au catalyzed cyclization giving the scytonemin monomer, different Au complexes were screened to compare the reaction yields and efficiencies of the reaction. In all cases of the Au catalyzed cyclization, 6-endo-dig products were obtained.

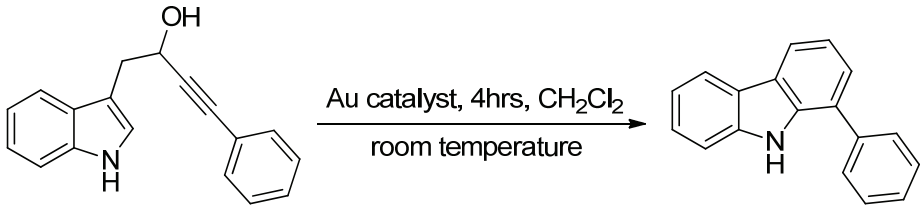
Table 3.3.1 Au catalysts and yields for Au catalyzed cyclization



Entry	Au catalysts	Yield
1	(chloro [tris (2,4-di-*tert*-butyl phenyl) phosphite]gold/$AgSbF_6$	35%
2	$AuCl_3/AgSbF_6$	25%
3	$AuCl_3$	45%
4	Acetonitrile[2-biphenyl-di-*tert*-butyl phosphine] gold (I)	68%

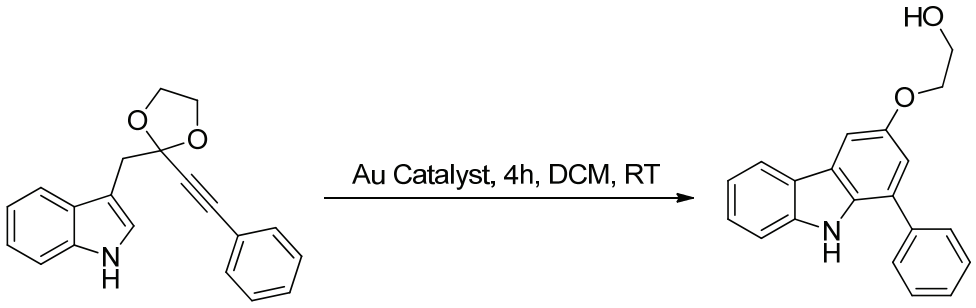
	hexafluoro antimonite	

Table 3.3.2 Reaction conditions for Au-catalyzed carbocyclization



Entry	Au catalysts	Yield
1	Acetonitrile[2-biphenyl-di-tert-butyl phosphine] gold (I) hexafluoro antimonite	not isolated, see reason in the discussion
2	$AuCl_3$	90%

Table 3.3.3 Reaction conditions for Au catalyzed cyclization.



Entry	Au catalyst	Yield
1	Acetonitrile[2-biphenyl-di-tert-butyl phosphine] gold (I)	23%

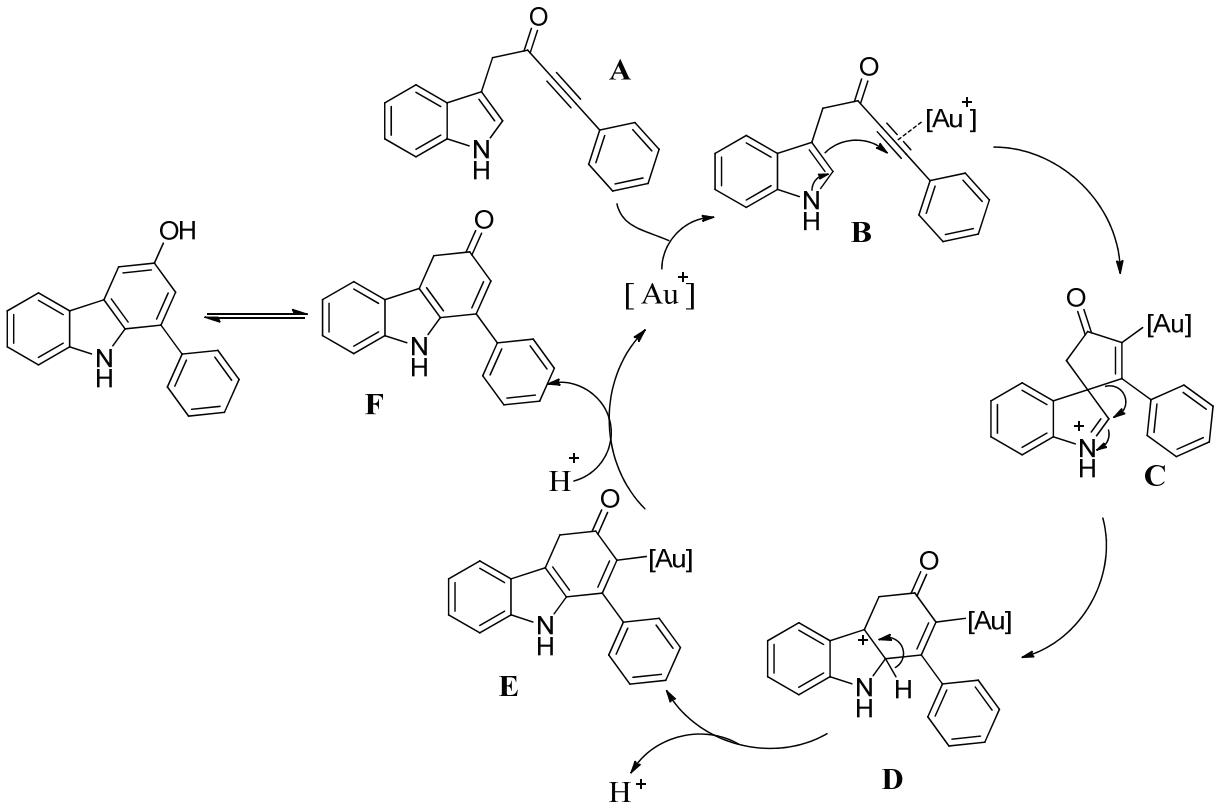
	hexafluoro antimonate	

For all catalytic systems, 6-endo-dig cyclizations were obtained. The table 3.3.1 above shows that ligand affects the reaction yield. The first entry with a mixture of (chloro [tris (2,4-di-tert-butyl phenyl) phosphite]gold and $AgSbF_6$ gave a yield of 35%. Entry 4 with Acetonitrile [2-biphenyl-di-tert-butyl phosphine] gold (1) hexafluoro antimonate gave the best yield of 68%. Both Au complexes are gold (I) complexes; the difference is that the latter is more electron rich than the former. From the table, an electron rich Au ligand gives a higher reaction yield compared to an electron poor Au ligand. Gold (III) complex was also screened using gold (III) chloride. Entry 3 using only gold (III) choride gave a reaction yield of 45%. Comparing entry 2 and 3, the presence of $AgSbF_6$ led to a lower reaction yield of 25%.

Attempts to reduce the electronic influence of the ketone on the triple bond was done in two ways. This was done to change the selectivity from 6-endo-dig to 5-exo-dig cyclization. The first way was by reducing the ketone to an alcohol, thus reducing the electron withdrawing effect. Au catalyzed cyclization was carried on the alkynol using different gold (I) and gold (III) catalysts. The product obtained was also a 6-endo-dig product, but this time followed by dehydration of the alcohol giving an aromatic system. From table 3.3.2 entry 1, no yield could be presented because the product was obtained in good yield according to NMR but could not be isolated in pure form. The excess weight of the product might be due to error from the weighing. Entry 2 with gold (III) chloride as gold (III) catalyst gave a reaction of 90%. In both cases, the reactions were clean with relatively high yields.

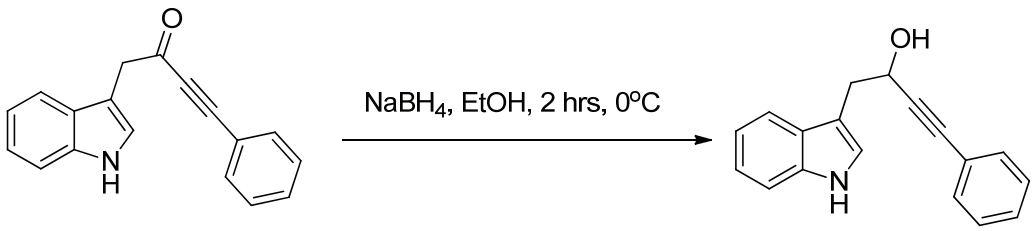
Table 3.3.3 shows the result of the second method. In this approach the electronic effect of the ketone was altered by acetal formation,which at the same time introduced a larger steric encumbrance. Comparing the yields of the different Au catalysts was not possible, because of the small amount of product obtained from the acetal formation. Acetonitrile[2-biphenyl-di-tert-butyl phosphine] gold (I) hexafluoro antimonate was used in this case because of the records of high yields from previous Au catalyzed reactions. The product obtained was also a 6-endo-dig product which gave a reaction yield of 23%.

From the results obtained above, irrespectively of the gold (I) or (III) catalyst used, reduction to alcohol or acetal formation, the reaction gave the more thermodynamically stable product, which is the 6-endo-dig product. This is the basic skeleton of another family of natural products known as carbazoles. A proposed mechanism for the 6-endo-dig product is illustrated in **scheme 3.3.1.**



Scheme 3.3.1. Proposed Au-catalyzed mechanism for 6-endo-dig

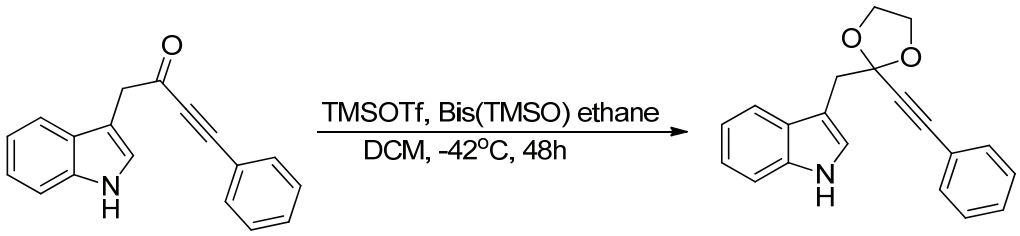
3.4 Reduction to alcohol



Scheme 3.4.1. Reaction condition for reduction to alcohol.

Reduction of alcohol can be viewed in any classical organic textbook.[45] $NaBH_4$ as the reducing agent undergoes a nucleophilic attack on the alkynone to give alcohol. This reaction gave a reaction yield of 35%. The formation of by-products during the reaction, made the purification complex which gave a low reaction yield.

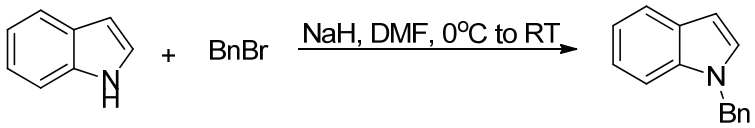
3.5 Acetal formation



Scheme 3.5.1. Reaction condition for acetal formation.

Acetal formation was done to introduce a steric bulk and also to reduce the electronic effect of the ketone on the alkyne. The aim of the reaction was to drive the reaction to give a 5-exo-dig or 6-endo-dig product. Acetal formation can be read about in any classical organic textbook.[46] The procedure seems quite easy to follow, but the reaction was very challenging. Previous studies carried out using similar substrates have shown that the reaction is challenging. The first attempt on this reaction failed with the product decomposing. No product was observed after purification. The second attempt gave a reaction yield of 29% after purification, but the product was impure. A second purification had to be done giving a reaction yield of 10%. The major problem of this reaction is the fast decomposition of the product, which makes purification complex leading to a very low yield and impure NMR spectra.

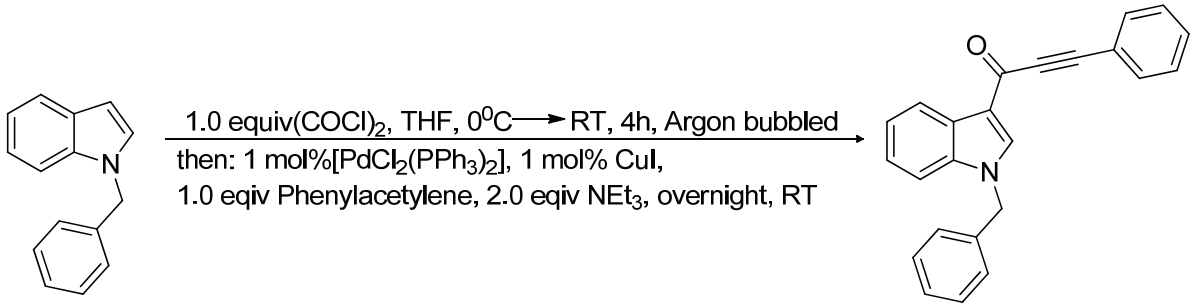
3.6 Indole *N*-protection



Scheme 3.6.1. Reaction condition for indole *N*-protection.

Indole *N*-protection was carried out on the indole via a nucleophilic attack on benzyl bromide. Previous study carried out by Norrio Shibata et al. in 2011 gave 88 % yield.[49] Two attempts of Indole *N*-protection gave yields of 72 % and 98%, respectively. Previous study and the reactions carried out in this report showed that the reaction was simple to carry out.

3.7 Decarbonylative Sonogashira Coupling



Scheme 3.7.1. Reaction conditions for decarbonylative Sonogashira coupling.

Previous studies of consecutive three-component synthesis of alkynones by decarbonylative Sonogashira coupling reported by Merkul and co-workers in 2009 gave a yield of 85 %.[33] Two attempts of decarbonylative Sonogashira coupling were carried which gave reaction yields of 67 % and 80 % respectively. This reaction was very tricky to handle because of its sensitivity to oxygen. Argon was continuously bubbled through the reaction mixture to avoid oxygen interfering with the reaction.

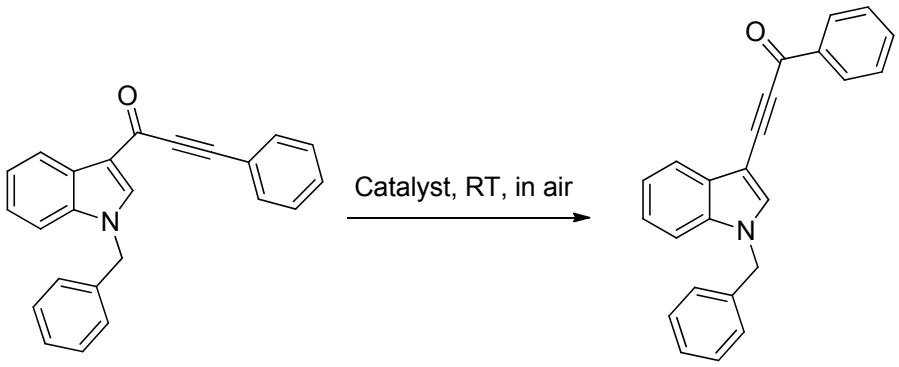
3.7.1 Suitable reaction condition

Consecutive three-component synthesis of alkynones by decarbonylative Sonogashira coupling was very challenging because of the sensitivity of the reaction to oxygen. Presence of oxygen in the reaction afforded the starting material and lots of 2-(1*H*-indol-3-yl) acetic acid as products. Several failed attempts were carried out changing the reaction conditions each time. Finally a decarbonylative Sonogashira coupling was achieved by bubbling argon throughout to remove oxygen from the reaction.

3.8 Au catalyzed isomerisation

Gold-catalyzed isomerization of indole was carried out using different gold catalysts and different (polar and non-polar) solvents. Below is a table of the result obtained from the reactions.

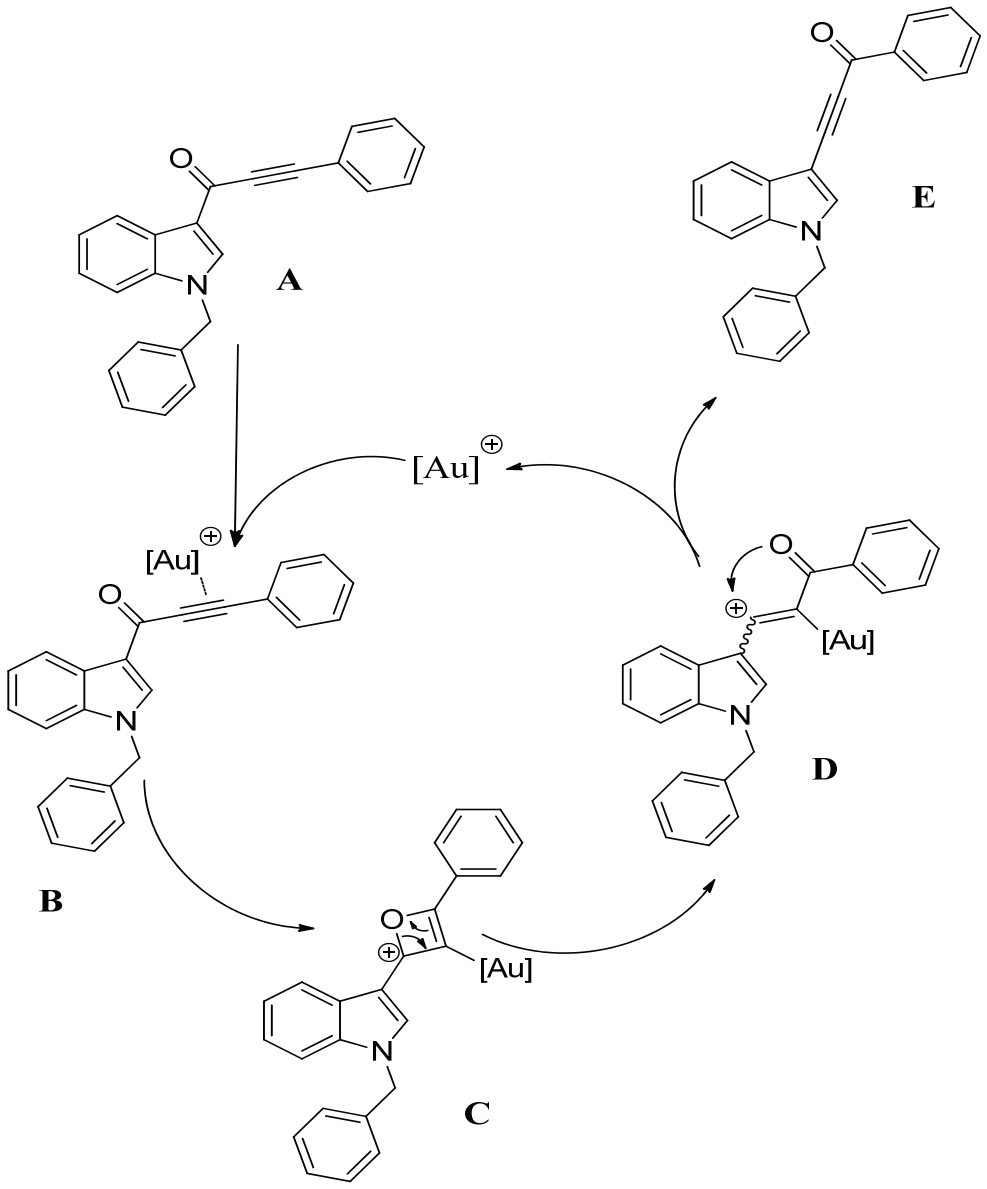
Table 3.8.1 Reaction conditions for Au-catalyzed isomerization



Entry	Catalyst	Solvent	Time [h]	Yield [%]
1	**A**	CH_2Cl_2	4	traces
2	**A**	CH_2Cl_2	25	57
3[a]	**A**	CH_2Cl_2	5	12
4	**B**	CH_2Cl_2	24	15
5	**C**	CH_2Cl_2	24	n.r
6	**A**	Toluene	26	25
7	**B**	Toluene	48	traces
8	**C**	Toluene	24	n.r

A= Acetonitrile[2-biphenyl di-tert-butyl phosphine]gold (I) hexafluoroantimonate. **B**= (chloro[tris(2-4-di-tert-butyl phenyl) phosphite] gold/ $AgSbF_6$. **C**= $AuCl_3/AgSbF_6$. [a]= 40^oC.

The results above show that irrespective of the gold catalyst used (gold I and III), solvent (polar or non-polar), reaction time and temperature, the same rearranged product is obtained. This isomerization reaction is likely to be related to the Meyer-Schuster rearrangement. The structure of the starting material is likely the reason for the rearrangement process to be favoured over cyclization reaction. The low number of carbons and the linear arrangement around the triple bond restrains the reaction from forming a cyclised product. Compared to the 6-endo-dig product from the gold-catalyzed cyclization of 1-(1H-indol-3-yl)-4-phenylbut-3-yn-2-one which had an extra carbon. A proposed mechanistic cycle of this reaction is illustrated in **scheme 3.8.1.**



Scheme 3.8.1 Proposed mechanism for gold-catalyzed reaction

Using acetonitrile [2-biphenyl di-tert-butyl phosphine] gold (I) (**A**) with DCM and stirring at 25 h gave yields of 57 % (entry 2). Entry 1 and 3 gave lower yield irrespective of the temperature increase in entry 3. $AuCl_3$ and $AgSbF_6$ using both DCM and toluene as solvent (entry 5 and 8) gave back the starting material. From the results gold (I) gave isomerized Au-catalyzed product while gold (III) gave no product. Low yields from gold-catalyzed reactions can be as a result of two factors.

i) **Life span of gold Catalyst**: The long period of reaction time can make the gold catalyst decompose leading to the small conversion of the product.

ii) **Reaction Equilibrium**: The ratio of the starting material to gold-catalyzed isomerization product from the NMR spectra shows the reaction might have reached to equilibrium and could no longer convert to the product leading to a low yield. At equilibrium the forward reaction is equal to the backward reaction.

Forward Rxn  Backward Rxn

4.0 Conclusion

The main objective of the project was to reduce the initial seven reaction steps of scytonemin monomer to three steps using gold catalyst. This was not achieved as the gold catalysed cyclization preceded regiospecifically to give the six-membered ring instead of the desired 5-membered, resulting in gold-catalyzed carbocyclization of indole to form carbazoles.

The second objective of the project was to synthesize nostodione via a gold catalysed cyclization. This was also not achieved as the gold catalysis proceeded to give isomerization of the α, β-unsaturated alkyne instead of cyclization. From the results obtained above, irrespectively of the gold (I) or (III) catalyst used, reduction to alcohol or acetal formation, *N*-protection of indole, polar or non-polar solvents, the reaction gave the thermodynamically more stable product, which is the 6-endo-dig product and isomerization of indole. The 6-endo-dig product is the basic skeleton of another class of natural products known as carbazoles.

4.1 Future work

The gold-catalyzed intramolecular carbocyclization and isomerization of indoles gave the most thermodynamically stable product of the 6-endo-dig cyclization and isomerization of the α, β-unsaturated alkyne. Future work should be carried out exploring more of the gold-catalyzed reactions because recent articles on gold catalysis showed gold catalyzed reactions gives rise to various interesting products.

5.0 Experimental section

5.1 General procedures

All reactions were carried out under argon atmosphere with dry solvents in oven dried glassware, unless otherwise noted. Dry terahydrofuran (THF) was obtained through distillation over sodium and benzophenone. Dry methylene chloride (DCM), triethyl amine (Et_3N) and toluene were obtained through distillation over calcium hydride. *N*,*N´*-dimethylformamide (DMF) was purchased in anhydrous form and used without further purification. Acetone, ethyl acetate (EtOAc) and petroleum ether (40-65^oC) were bought from commercial vendors and used as received. Reagents were bought from commercial vendors and used as received, unless otherwise stated.

Reactions were monitored by thin-layers chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent. Merck silica gel Geduran 60 (particle size 0.063 – 0.200 mm) was used for flash column chromatography. NMR spectra were recorded on Jeol Eclipse 400 MHz instrument and calibrated using residual undeuterated chloroform (1H δ = 7.26 ppm, 13C δ = 77.36 ppm) as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad.

5.2 Synthesis of 2-(1H-Indole-3-yl)-N-methoxy-N-methylacetamide (2)

3-Indoleacetic acid (10.0 g, 57.1 mmol) and *N*-methylmorpholine (6.4 ml, 58.2 mmol) were dissolved in THF (96 ml). The stirred mixture was cooled to -20^oC, isopropyl chloroformate (60.8 ml, 60.8 mmol) was added dropwise, and the reaction was stirred for 30 min at -20^oC. The temperature was then raised to 0^oC, a suspension of *N*,*O*-dimethylhydroxylamine hydrochloride (6.82 g, 69.9 mmol) and Et_3N (8.96 ml, 64.7 mmol) in DMF (57.6 ml) was added, and the remnant was rinsed with DMF (57.6 ml). After being stirred for 1 h at 0^oC, the reaction was quenched with water (480 ml). The phases were separated, and the aqueous phase was extracted with EtOAc (3x200 ml). The combined organic layers were washed with HCl (aq) (1 M, 480 ml), saturated aqueous $NaHCO_3$ (480 ml) and brine (480 ml). The organic phase was dried over $NaSO_4$, filtered and concentrated under reduced pressure.

The crude product was purified by flash chromatography (EtOAc/Petroleum ether, 4:1) to obtain **2** (8.75 g, 70%) as beige crystals. ^{1}H NMR ($CDCl_3$) δ (ppm) 3.22 (s, 3H), 3.66 (s, 3H), 3.92 (s, 2H), 7-10-7.20 (m, 3H), 7.32 (d, J = 8.06 Hz, 1H), 7.65 (d, J = 7.69 Hz, 1H), 8.21 (br s, 1H).

5.3 Synthesis of 1-(1H-indol-3-yl)-4-phenylbut-3-yn-2-one (3)

A solution of *n*-BuLi (2.5 M in hexane, 3.2 ml, 8.0 mmol) was added to a solution of phenyl acetylene (1.0 ml, 9.2 mmol) in THF (10.88 ml) at -78^{o}C. The reaction mixture was stirred for 1 h at -78^{o}C, the mixture was then warmed to room temperature and stirred for 15 min. The reaction mixture was recooled to -78^{o}C followed by addition to a solution of the Weinreb amide **2** (0.50 g, 2.3 mmol) in THF (31.8 ml) via a syringe at -78^{o}C. The reaction mixture was stirred for an additional 30 min and warmed to room temperature. The reaction was quenched after 75 min by cooling the reaction mixture to -78^{0}C followed by addition of 50 ml of saturated aqueous $NaHSO_4$. The mixture was extracted with EtOAc (3x40 ml) and the combined organic phases were washed with brine (80 ml), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (EtOAc/Petroleum ether, 1:1) to obtain **3** (0.48 g, 80%) as pale yellow crystals. ^{1}H NMR ($CDCl_3$) δ (ppm) 4.09 (s, 2H), 7.15-7.23 (m, 3H), 7.29-7.42 (m, 6H), 7.67 (d, J = 7.32 Hz, 1H), 8.16 (br s, 1H)

5.4 Synthesis of 1-Phenyl-9H-carbazol-3-ol (4)

General procedure A: Under Argon atmosphere, catalyst (0.02 mmol, 10 mol %) was put in a flask and dissolved in CH_2Cl_2 (5 ml). A solution of alkyne **3** (51.7 mg, 0.2 mmol, 1 equiv) in CH_2Cl_2 (1 ml) was added via a syringe to the stirred solution of gold catalyst. The reaction mixture was stirred for 4 h at room temperature. The crude reaction mixture was poured directly on top of a short silica plug and eluated with EtOAc. The solution was concentrated under reduced pressure. The crude product was purified by flash column chromatography in DCM to obtain **4** as brown crystals. ^{1}H NMR ($CDCl_3$) δ (ppm) 4.89 (br s, 1H), 7.02 (d, J = 2.20 Hz, 1H), 7.19-7.23 (m, 1H), 7.36-7.47 (m, 3H), 7.50 (d, J = 2.56 Hz, 1H), 7.54 (t, J = 15.01 Hz, 2H), 7.66 (d, J = 7.32 Hz, 2H), 8.01 (d, J = 8.02 Hz, 1H), 8.14 (s, 1H)

General procedure A using (chloro[tris (2, 4-di-tert-butyl phenyl) phosphate] gold (18.3 mg) and $AgSbF_6$ (7.2 mg) gave yield of 35%.

General procedure A using $AuCl_3$ (6.8 mg) and $AgSbF_6$ (7 mg) gave yield of 26%.

General procedure A using $AuCl_3$ (6.2 mg) gave yield of 45%.

General procedure A using Acetonitrile [2-biphenyl) di-tert-butyl phosphine] gold (I) hexafluoroantimonate (17.8 mg) gave yield of 68%

5.5 Synthesis of 1-(1H-indol-3-yl)-4-phenylbut-3-yn-2-ol (5)

To a 0.01 M solution of alkyne **3** (276 mg, 1.1 mmol) in ethanol (107 ml), $NaBH_4$ (40 mg, 1.1 mmol) was added. The reaction mixture was stirred for 2 h at 0^oC and quenched with HCl (aq.) (50 ml) and brine (200 ml). The aqueous phase was extracted with EtOAc (50 ml) and DCM (50 ml). The combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (DCM) to obtain **5** (97.2 mg, 35%) as brown crystals. ^1H NMR ($CDCl_3$) δ (ppm) 2.24 (s, 1H), 3.24-3.37 (m, 2H), 4.90 (br s, 1H), 7.14-7.18 (m, 2H), 7.21-7.25 (m, 1H), 7.27-7.33 (m, 3H), 7.36 (s, 1H), 7.38-7.42 (m, 2H), 7.74 (d, J = 7.32 Hz, 1H), 8.13 (s, 1H)

5.6 Synthesis of 1-Phenyl-9H-carbazole (6)

General procedure B: Under Argon atmosphere, gold catalyst (0.02 mmol, 10 mol %) was put in a flask and dissolved in CH_2Cl_2 (5 ml). A solution of alkyne **5** (48.6 mg, 0.2 mmol, 1 equiv) in CH_2Cl_2 (1 ml) was added via a syringe to the stirred solution of gold catalyst. The reaction mixture was stirred for 4 h at room temperature. The crude reaction mixture was poured directly on top of a short silica plug and eluated with EtOAc. The solution was concentrated under reduced pressure. The crude product was purified by flash column chromatography (Petroleum ether/DCM, 3:2) to obtain **6** as brown crystals. ^1H NMR ($CDCl_3$) δ (ppm) 7.25-7.29 (m, 1H), 7.34 (t, J = 7.69 Hz, 7.32 Hz, 1H), 7.41-7.47 (m, 4H), 7.57 (t, J = 8.06 Hz, 7.32 Hz, 2H), 7.71 (d, J = 6.96 Hz, 2H), 8.11 (q, J = 7.69 Hz, 6.22 Hz, 8.06 Hz, 2H), 8.32 (s, 1H)

General procedure B using Acetonitrile [2-biphenyl) di-tert-butyl phosphine] gold (I) hexafluoroantimonate (17.8 mg) gave pure product.

General procedure B using $AuCl_3$ gave yield of 90%.

5.7 Synthesis of 3-((2-(phenylethynyl)-1, 3-dioxolan-2-yl) methyl)-1H-indole (7)

To a solution of alkyne **3** (462 mg, 1.8 mmol) in DCM at -78°C were added 1,2-Bis(trimethylsilyloxy)ethane (2.14 ml, 8.91 mmol) and TMSOTf (32.2 µl, 0.18 mmol). The solution was let warm to -42°C, stirred for 48 h and then quenched with a mixture of pyridine (8 ml) and saturated aqueous $NaHCO_3$ (20 ml). The aqueous layer was extracted with EtOAc (3x60 ml) and the combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure to a brown oil. The crude product was purified by flash chromatography (Petroleum ether/EtOAc, 1:1) to obtain **7** (53 mg) as white crystals. The product obtained was impure due to rapid decomposition of the product, but some peaks could be noticed from the spectra. ^{1}H NMR ($CDCl_3$) δ (ppm), 3.48 (s, 2H), 3.95-3.99 (m, 2H), 4.14-4.16 (m, 2H), 7.09-7.19 (m, 5H), 7.79 (d, J = 8.06 Hz, 1H), 8.08 (br s, 1H)

5.8 Synthesis of 2-((1-phenyl-9H-carbazol-3-yl) oxy) ethanol (8)

Under Argon atmosphere, Acetonitrile [2-biphenyl) di-tert-butyl phosphine] gold (I) hexafluoroantimonate (18.4 mg, 0.02 mmol, 10 mol %) was put in a flask and dissolved in CH_2Cl_2 (5 ml). A solution of alkyne **7** (53 mg, 0.2 mmol, 1 equiv) in CH_2Cl_2 (1 ml) was added via a syringe to the stirred solution of the gold catalyst. The reaction mixture was stirred for 4 h at room temperature. The crude reaction mixture was poured directly on top of a short silica plug and eluated with EtOAc. The solution was concentrated under reduced pressure. The crude product was purified by flash column chromatography (Petroleum ether/EtOAc, 1:1) to obtain **8** (12 mg). The compound was impure but some peaks were noticeable when compared with ^{1}H NMR of **4**. ^{1}H NMR ($CDCl_3$) δ (ppm) 4.03 (t, J = 4.56 Hz, 4.59 Hz, 2H), 4.25 (t, J = 4.56 Hz, 4.59 Hz, 2H), 7.13 (d, J = 2.20 Hz, 1H), 7.20-7.24 (m, 1H), 7.39-7.46 (m, 3H), 7.55 (t, J = 7.69 Hz, 7.32 Hz, 2H), 7.59 (d, J = 2.56 Hz, 1H), 7.67-7.69 (m, 2H), 8.04 (d, J = 8.06 Hz, 1H), 8.18 (br s, 1H)

5.9 Synthesis of 1-benzyl-1*H*-indole (9)

Indole (2.1098 g, 18.00 mmol, 1 eq), dry DMF (18.0 ml) and NaH (867.0 mg, 60 % suspension in mineral oil, 21.67 mmol, 1.2 eq) was added portion-wise under argon atmosphere at 0°C. The reaction mixture was then warmed to room temperature and stirred for 30 min. After

cooling to 0°C, BnBr (2.4 ml, 20.07 mmol, 1.1 eq) was added drop-wise to the reaction mixture. The reaction mixture was warmed to room temperature and stirred overnight. The reaction was quenched by adding water (75 ml) and the aqueous phase was extracted with Et_2O (3 x 50 ml). The combined organic layers were washed with brine (50 ml), dried over anhydrous $NaSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (Petroleum ether/EtOAc, 3:1) to obtain **9** as a brown crystals (3.8 g, 98 %). ^{1}H NMR ($CDCl_3$) δ (ppm) 5.35 (s, 2H), 6.61 (d, J = 2.93 Hz, 1H), 7.11 – 7.45 (m, 9H), 7.71 (d, 1H)

5.10 Synthesis of 1-(1-benzyl-1H-indol-3-yl)-3-phenylpro-2-yn-1-one (10)

N-Benzyl-1H-indole (0.50 g, 2.4 mmol) in dry THF (12.1 ml) was placed under argon in a screw-cap vessel with septum, argon was bubbled through and cooled to 0°C (water/ice). Then, oxalyl chloride (0.2 ml, 2.4 mmol) was added to the reaction mixture at 0°C. The mixture was allowed to come to room temperature and was stirred for 4 h. Then, $PdCl_2(PPh_3)_2$ (17.3 mg, 0.02 mmol), CuI (4.9 mg, 0.02 mmol), phenylacetylene (0.3 ml, 2.4 mmol), and dry triethylamine (0.7 ml, 4.8 mmol) were successively added to the mixture and stirring at room temperature was continued for 48 h. The evolution of CO could be observed. Saturated brine (2x25 mL) was added, and the mixture was extracted with DCM (4 x 25 mL). The combined organic layers were dried with anhydrous sodium sulphate. The crude product was purified by flash column chromatography (DCM) to obtain **10** as brown solid (650.9 mg, 80 %). ^{1}H NMR ($CDCl_3$) δ (ppm), 5.40 (s, 2H), 7.19 – 7.21 (m, 2H), 7.27 – 7.48 (m, 10H), 7.61 – 7.65 (m, 2H), 8.03 (s, 1H), 8.45 – 8.47 (m, 1H)

5.11 Synthesis of 3-(1-benzyl-1H-indol-3-yl)-1-phenylprop-2-yn-1-one (11)

General procedure C: Catalyst (0.02 mmol, 10 mol %) were mixed in a flask and dissolved in CH_2Cl_2 or toluene (5 ml). A solution of alkyne **10** (67 mg, 0.2 mmol, 1 equiv) in CH_2Cl_2 or toluene (1 ml) was added via a syringe to the stirred solution catalyst. The reaction mixture was stirred at room temperature for the time indicated in table 3.8.1. The crude reaction mixture was poured directly on top of a short silica plug and eluated with EtOAc. The crude product was purified by flash column chromatography using EtOAc/Petroleum ether and DCM at different ratios to obtain **11** as brown crystals. ^{1}H NMR ($CDCl_3$) δ (ppm), 5.36 (s, 2H), 7.16 – 7.21 (m, 2H), 7.29 – 7.38 (m, 6H), 7.51 – 7.56 (m, 2H), 7.60 – 7.65 (m, 1H), 7.67 (s,

1H), 7.89 – 7.94 (m, 1H), 8.27 – 8.32 (m, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm) = 50.9, 53.5, 90.6, 92.4, 95.0, 110.8, 120.5, 122.0, 123.8, 127.2, 128.4, 128.6, 129.2, 129.5, 129.7, 133.6, 136.2, 136.4, 137.4, 178.0.

General procedure C, using Acetonitrile [2-biphenyl) di-tert-butyl phosphine] gold (I) hexafluoroantimonate (17.7 mg) and DCM as solvent. The reaction mixture was stirred for 25 h gave 57% yield.

General procedure C, using Acetonitrile [2-biphenyl) di-tert-butyl phosphine] gold (I) hexafluoroantimonate (17.7 mg) and DCM as solvent. The reaction mixture was stirred for 5 h at 40^{o}C gave 13% yield.

General procedure C, using (chloro[tris (2, 4-di-tert-butyl phenyl) phosphate] gold (17.7 mg) and $AgSbF_6$ (7.1 mg). DCM was used as solvent and the reaction mixture was stirred for 24 h gave yield of 15%.

General procedure C, using Acetonitrile [2-biphenyl) di-tert-butyl phosphine] gold (I) hexafluoroantimonate (17.7 mg) and toluene as solvent. The reaction mixture was stirred for 26 h gave 25% yield.

6. Acknowledgement

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7. References

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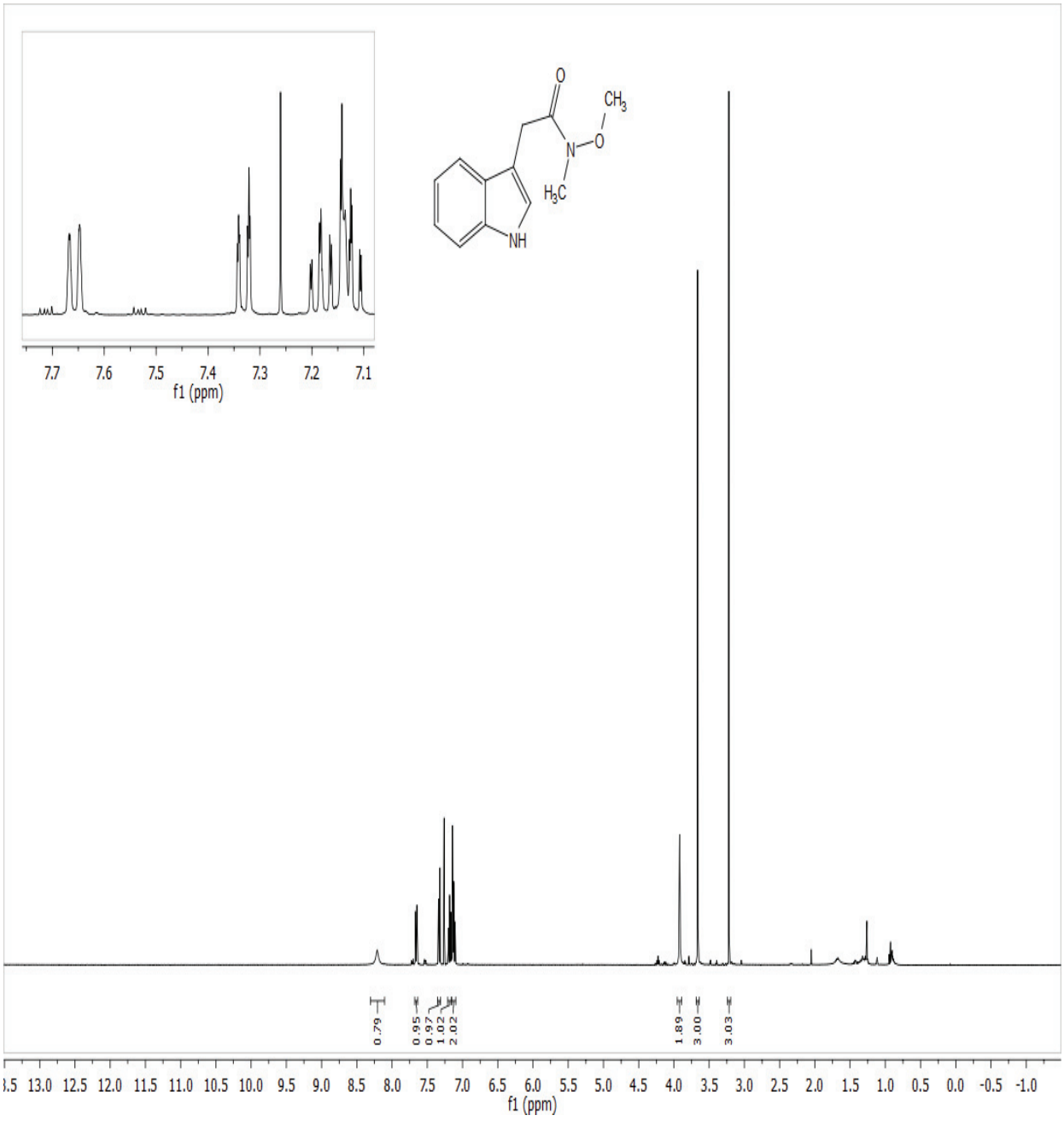
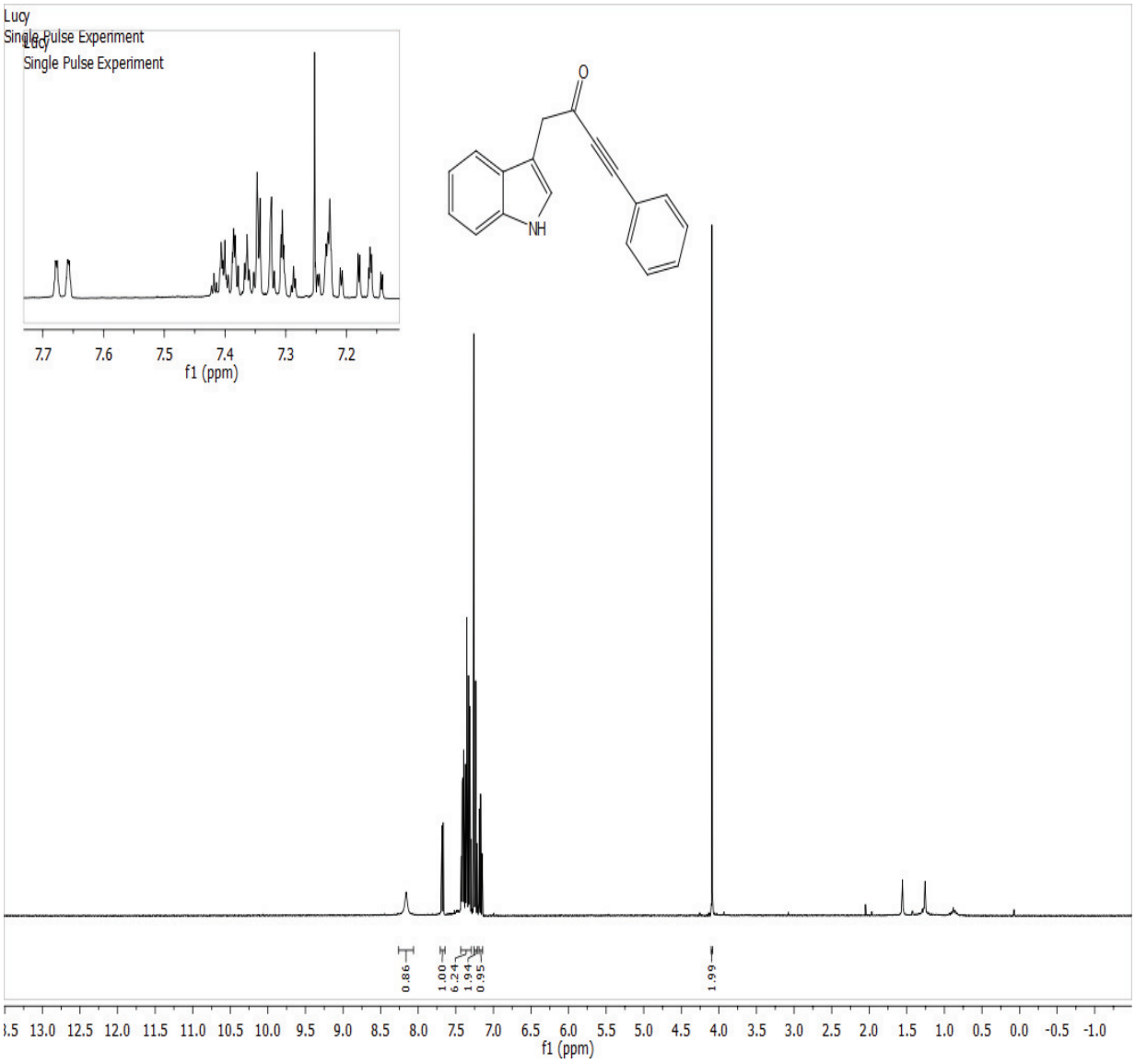
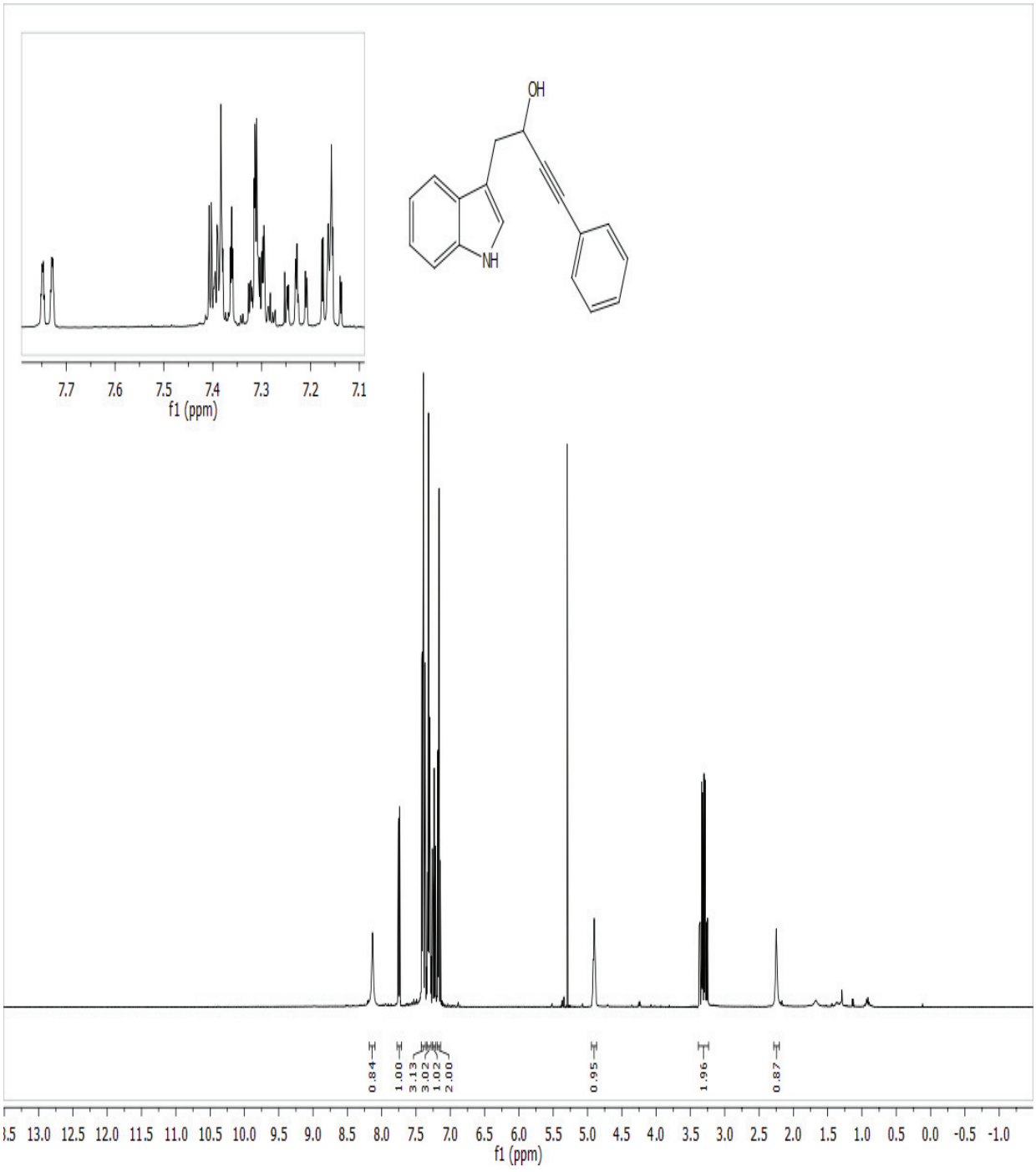
8. Appendix


O
CH3
N
O
H3C
NH
7.7
7.6
7.5
7.4
7.3
7.2
7.1
f1 (ppm)
0.79
0.95
0.97
1.02
2.02
1.89
3.00
3.03
13.0
12.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)


Lucy
Single Pulse Experiment
Lucy
Single Pulse Experiment
7.7
7.6
7.5
7.4
7.3
7.2
f1 (ppm)
O
NH
0.86
1.00
6.24
1.94
0.95
1.99
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)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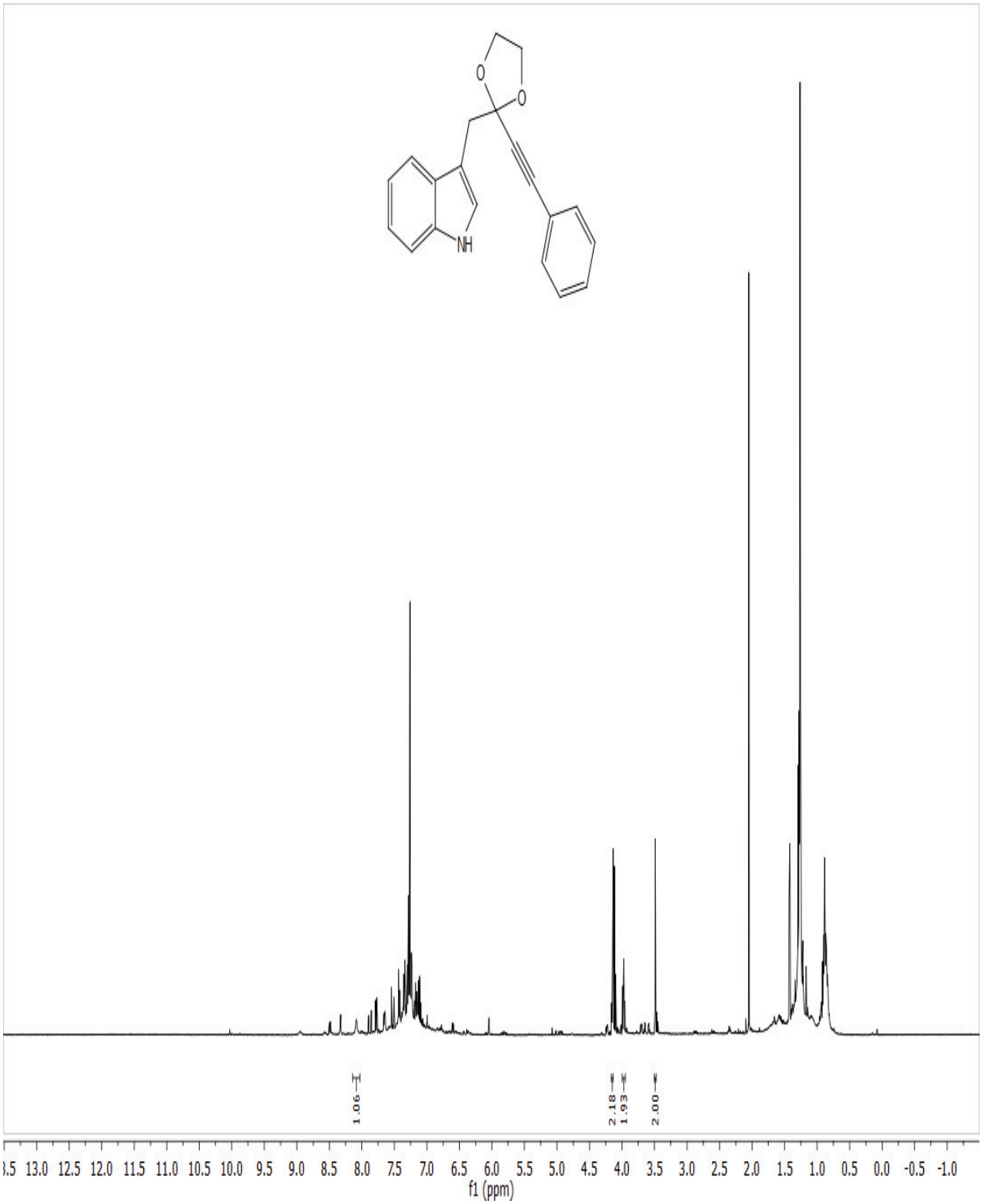
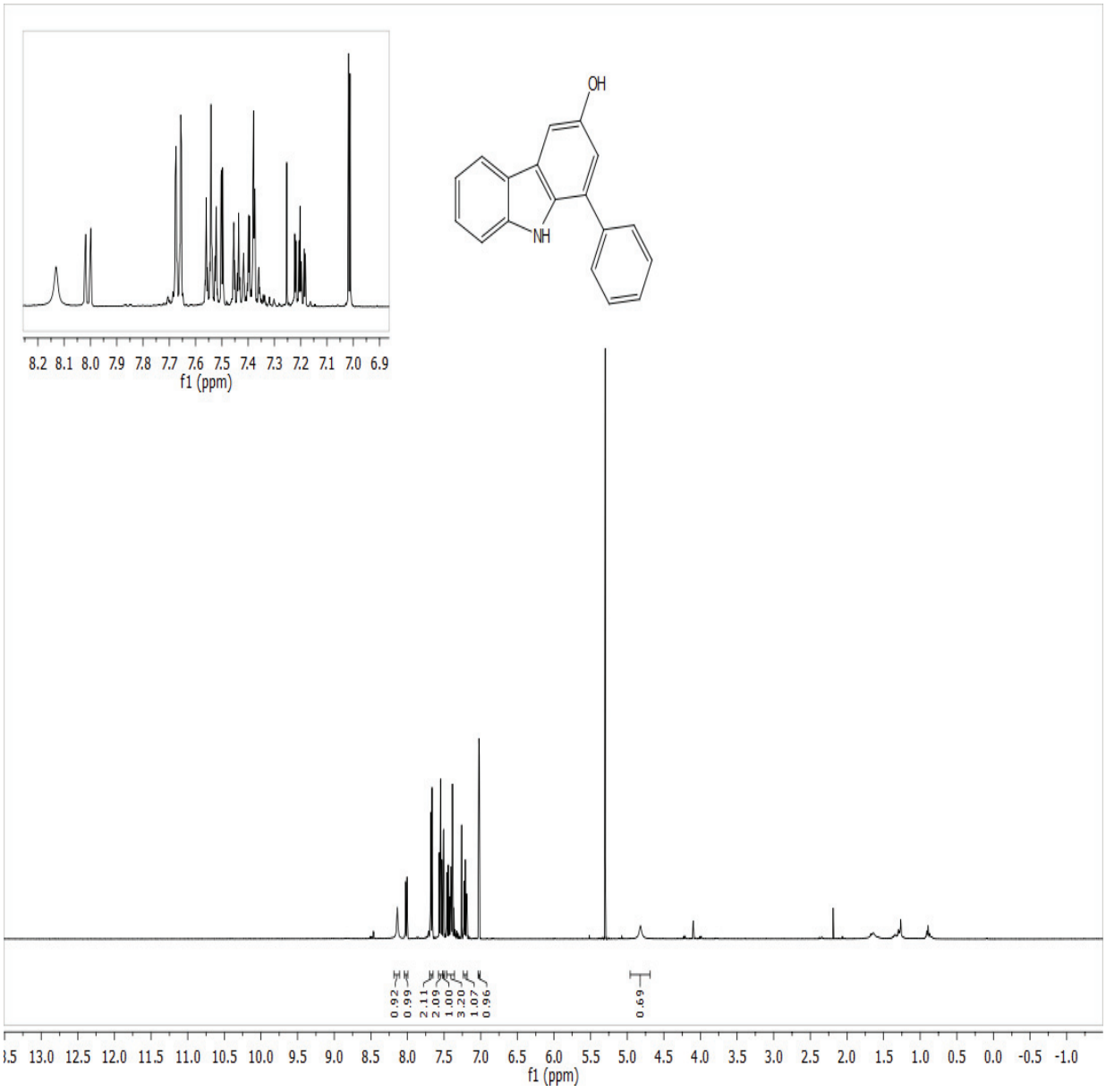
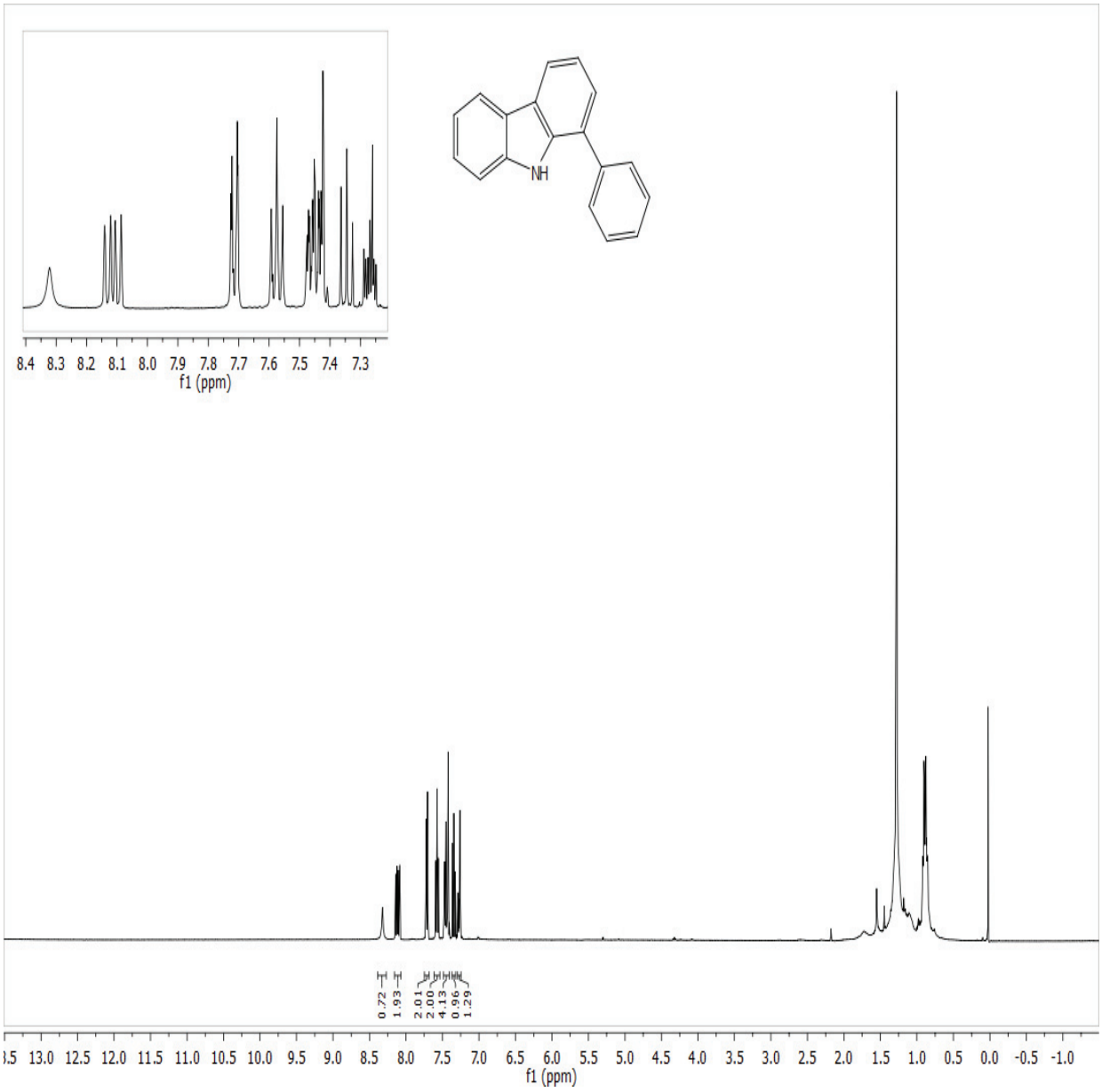
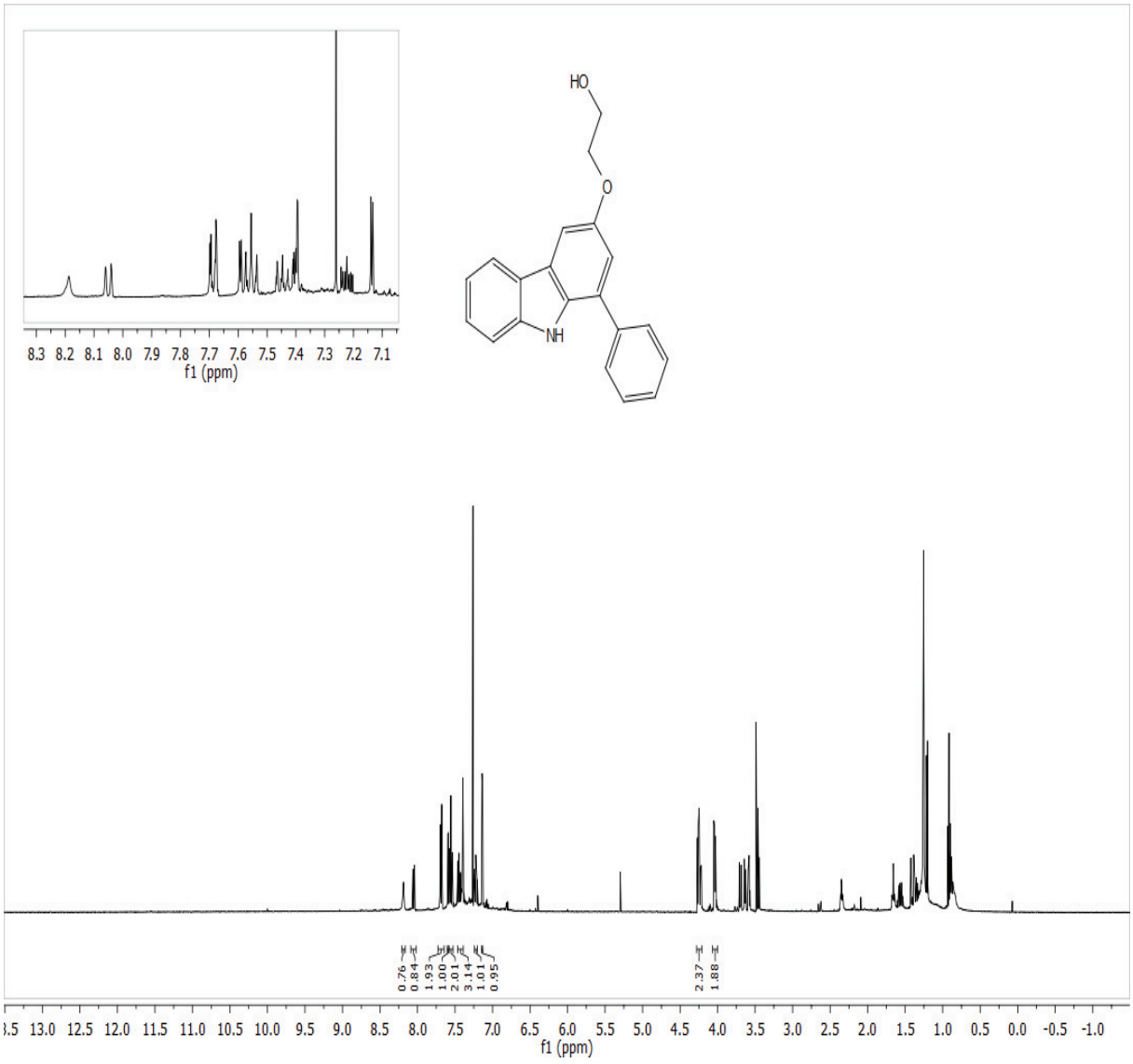
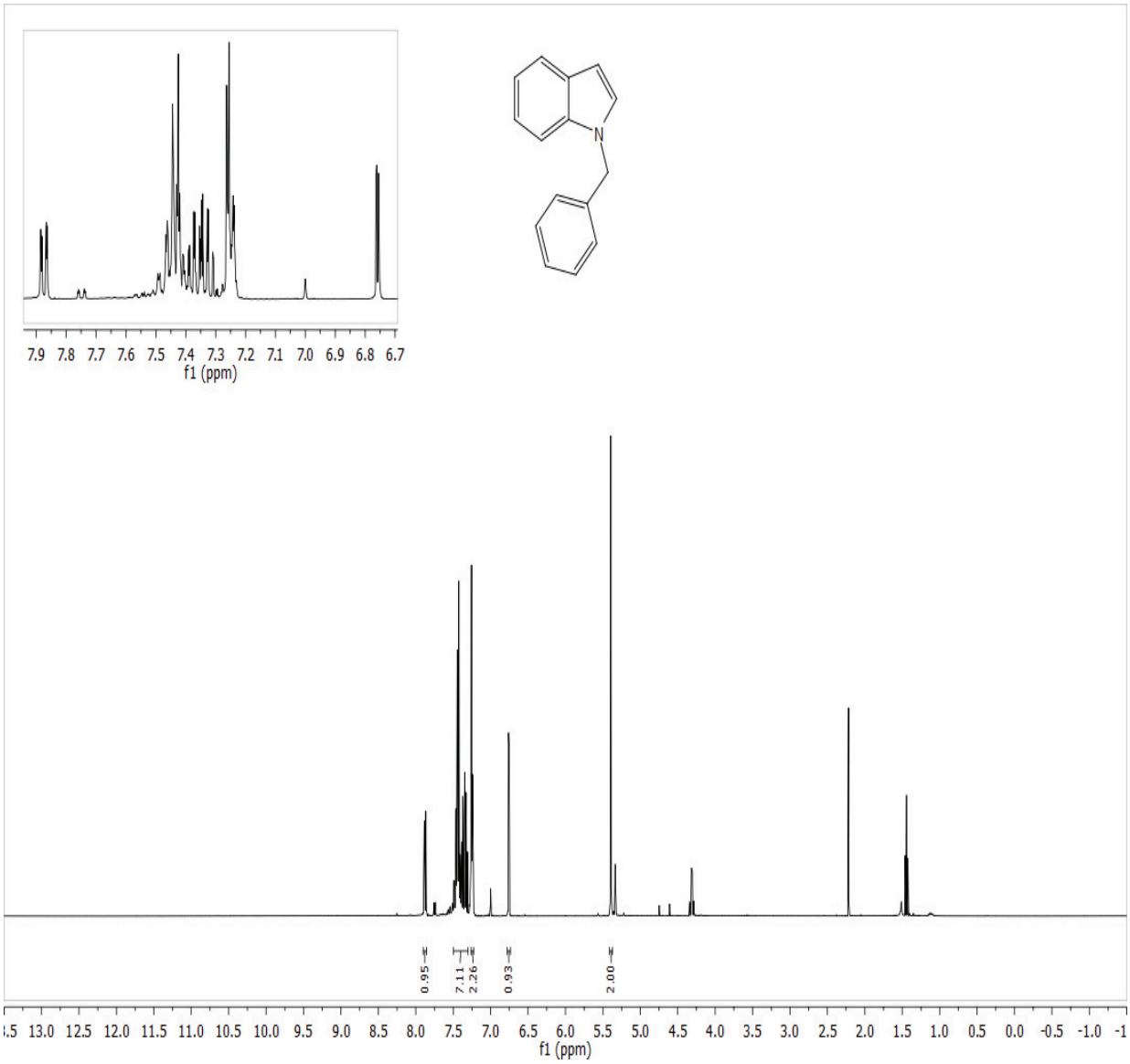
NH
7.7
7.6
7.5
7.4
7.3
7.2
7.1
f1 (ppm)
0.84
1.00
3.13
3.02
1.02
2.00
0.95
1.96
0.87
13.0
12.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)

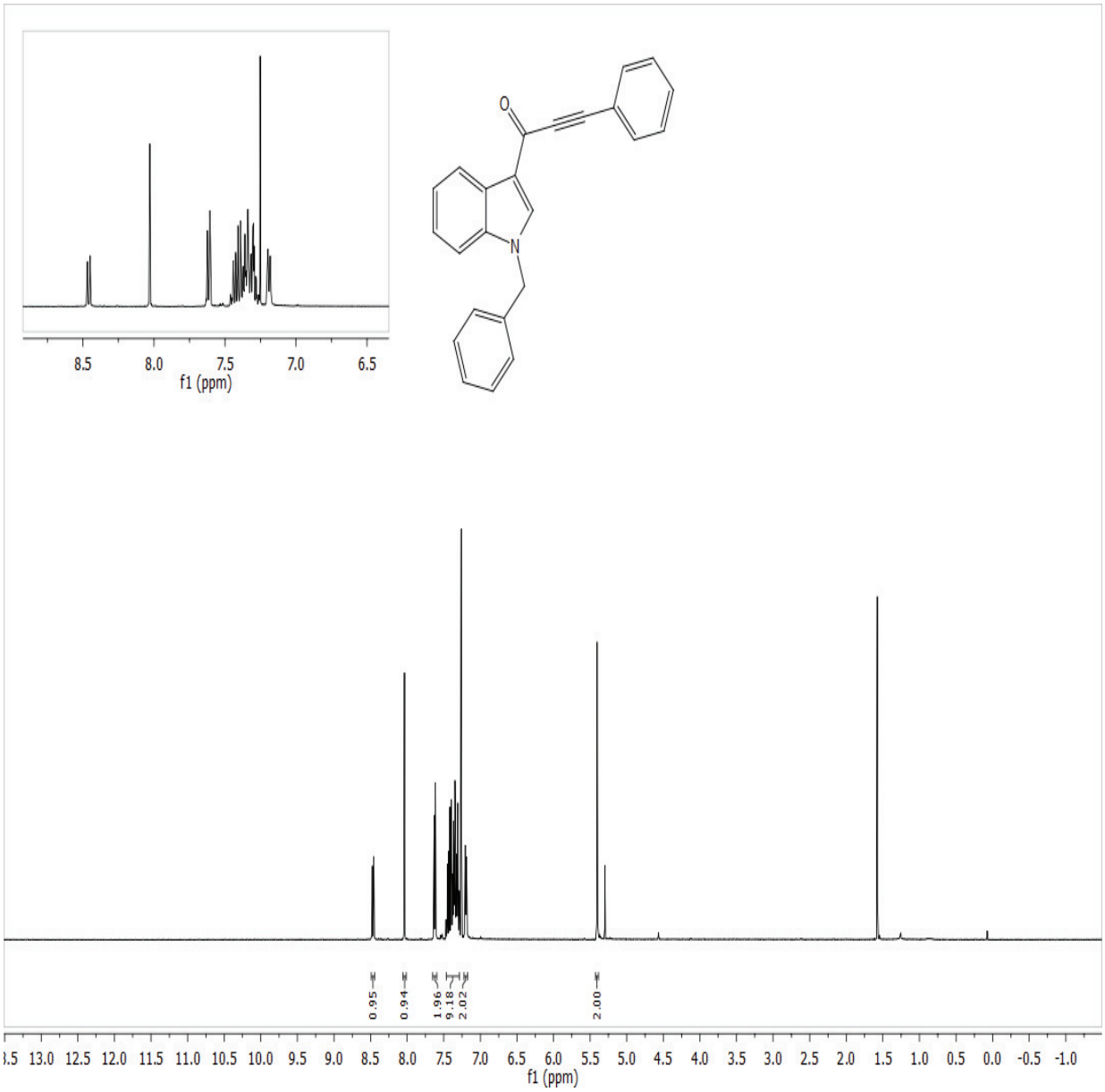

O
O
NH
1.06
2.18
1.93
2.00
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

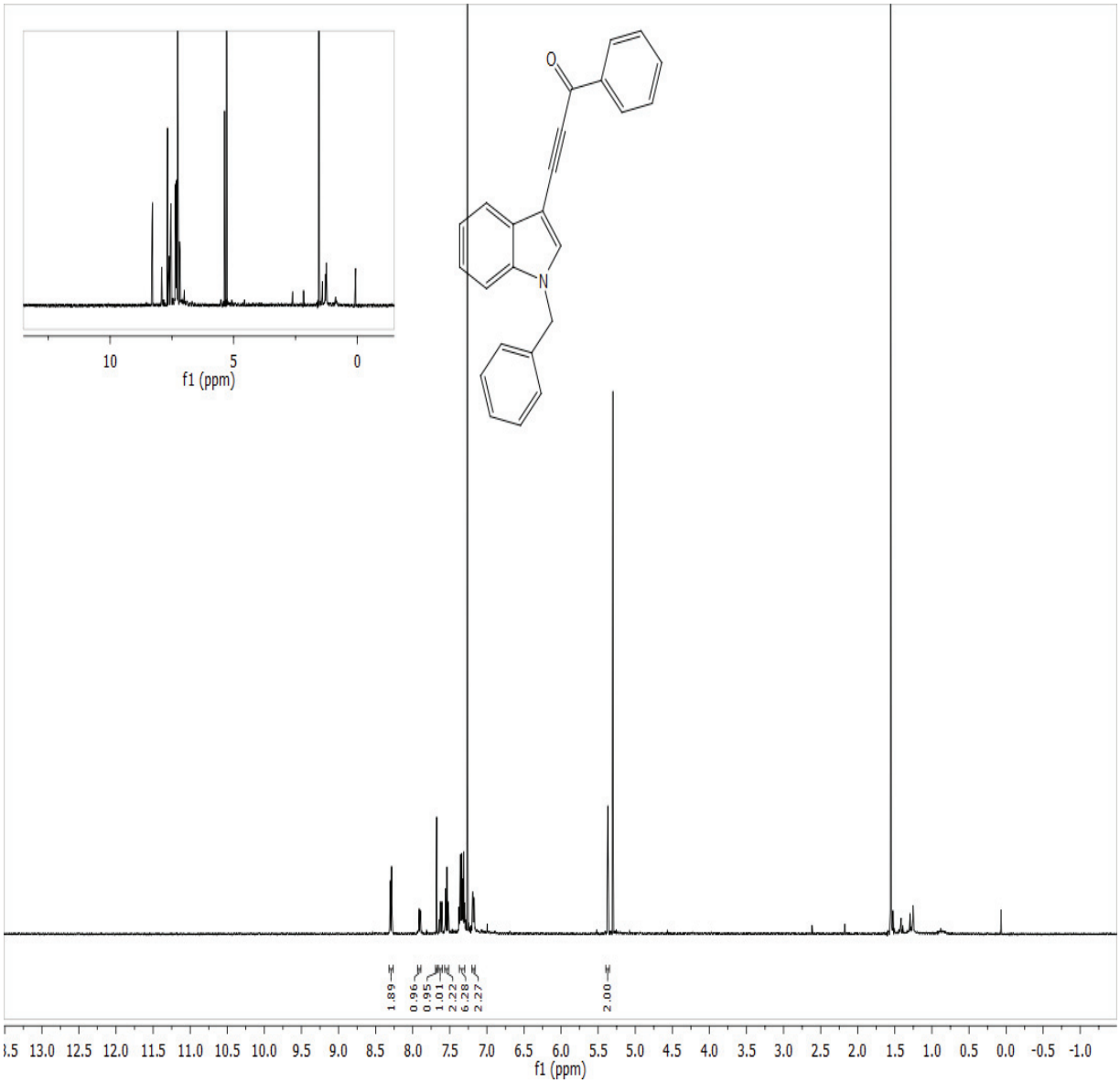

OH
NH
8.2 8.1 8.0 7.9 7.8 7.7 7.6 7.5 7.4 7.3 7.2 7.1 7.0 6.9
f1 (ppm)
0.92
0.99
2.11
2.09
1.00
3.20
1.07
0.96
0.69
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

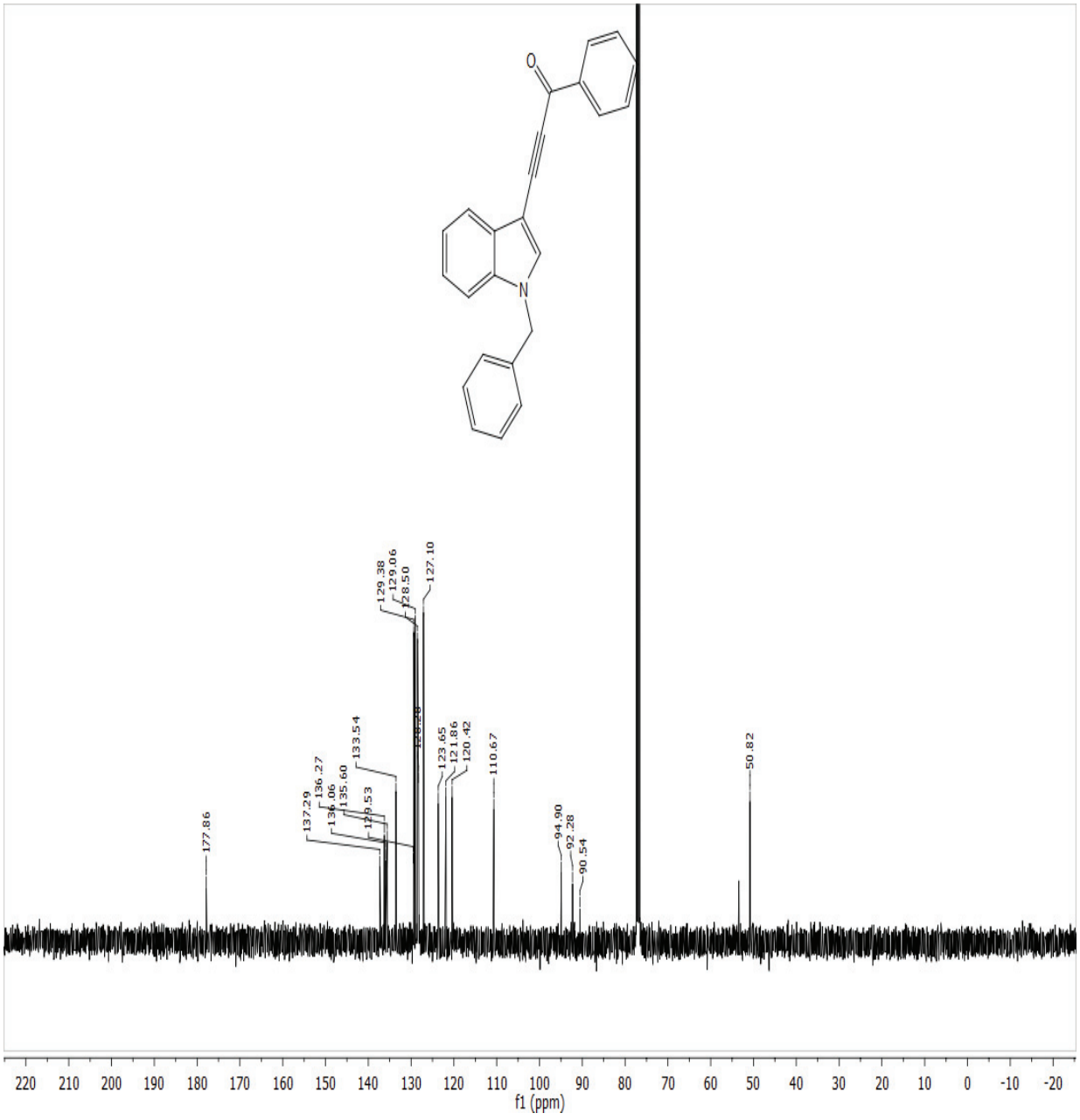

NH
8.4 8.3 8.2 8.1 8.0 7.9 7.8 7.7 7.6 7.5 7.4 7.3
f1 (ppm)
0.72
1.93
2.01
2.00
4.13
0.96
1.29
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)


HO
O
NH
8.3 8.2 8.1 8.0 7.9 7.8 7.7 7.6 7.5 7.4 7.3 7.2 7.1
f1 (ppm)
0.76
0.84
1.93
1.00
2.01
3.14
1.01
0.95
2.37
1.88
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)


N
7.9 7.8 7.7 7.6 7.5 7.4 7.3 7.2 7.1 7.0 6.9 6.8 6.7
f1 (ppm)
0.95
7.11
2.26
0.93
2.00
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)


O
N
8.5
8.0
7.5
7.0
6.5
f1 (ppm)
0.95
0.94
1.96
9.18
2.02
2.00
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)


O
N
10
5
0
f1 (ppm)
1.89
0.96
0.95
1.01
2.22
6.28
2.27
2.00
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)


O
N
177.86
137.29
136.27
136.06
135.60
133.54
129.53
129.38
129.06
128.50
127.10
123.65
121.86
120.42
110.67
94.90
92.28
90.54
50.82
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)