SYNOPSIS

The thesis entitled **"Synergistic Gold and Copper Dual Catalysis for Inter and Intramolecular Glaser-Hay Coupling: Application for Total Synthesis of Ivorenolide B and 1′,8′- Dihydroxy-3,4-dihydrovernoniyne"** has been divided into three chapters.

CHAPTER I: This chapter describes development of new methodology to Inter and Intramolecular Glaser-Hay coupling and its applications. This chapter is subdivided into three sections.

Section A: This section deals with the brief introduction on Glaser-Hay Coupling of Terminal Acetylenes (homo, hetero and macrocyclization).

Section B: This section describes application to Gold and Copper Synergistic Catalysis for Intermolecular Glaser-Hay Coupling of Terminal Alkynes.

Section C: This section describes application to Synergistic Gold and Copper Dual Catalysis for Intramolecular Glaser-Hay Coupling.

CHAPTER II: This chapter is further subdivided into two sections.

Section A: This section deals with the Brief Introduction and Previous Synthetic Approaches of Ivorenolides.

Section B: This section describes Total Synthesis of Ivorenolide B.

CHAPTER III: This chapter is further subdivided into two sections.

Section A: This section deals with the Brief Introduction and Previous Synthetic Approaches of Vernoniynes.

Section B: This section describes Total Synthesis of 1′,8′-Dihydroxy-3,4-dihydrovernoniyne.

CHAPTER I:

Section A: This section deals with the brief introduction on Glaser-Hay coupling of terminal acetylenes (homo, hetero and macrocyclization).

Section B: This section describes application to Synergistic/Cooperative Gold and Copper Dual Catalysis for Intermolecular Glaser-Hay Coupling.

Unsymmetrical 1,3-diynes structural motifs are very important building blocks in organic synthesis and material sciences. Their widespread application in organicmaterials, organometallics, and pharmaceutical industry has greatly attracted the synthetic chemist. Traditionally they could be prepared following Glaser-Hay coupling and Cadiot-Chodkiewicz coupling. Conventional Glacer-Hay coupling often suffers from undesired competing homocoupling and an excess amount of one alkyne is required. Cadiot-Chodkiewicz coupling requires alkyne pre-functionalization, however, usually suffers from undesired halogen-metal exchange reactions and poor selectivity. Indeed, the development of practical and efficient methods for the synthesis of 1,3-diynes has gained much attention. Several attempts were made to improve the efficiency of this reaction, such as Pd/Cu and Ni/Cu catalysis.

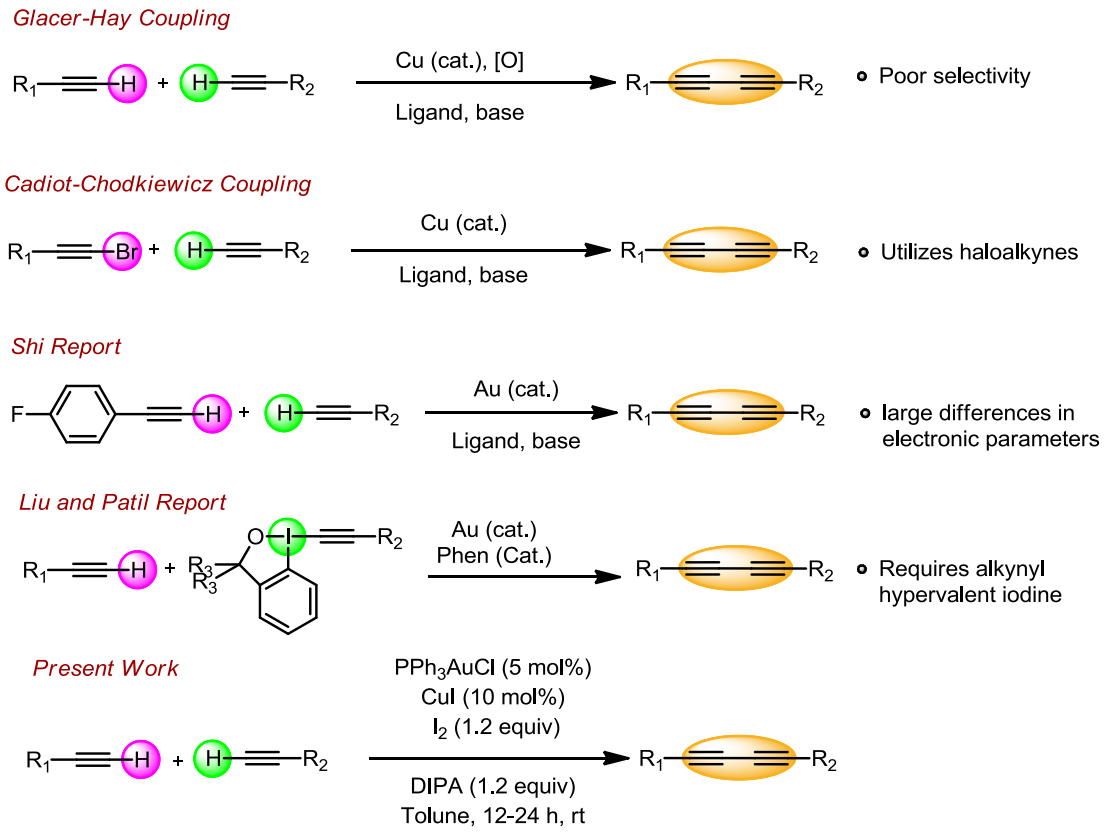
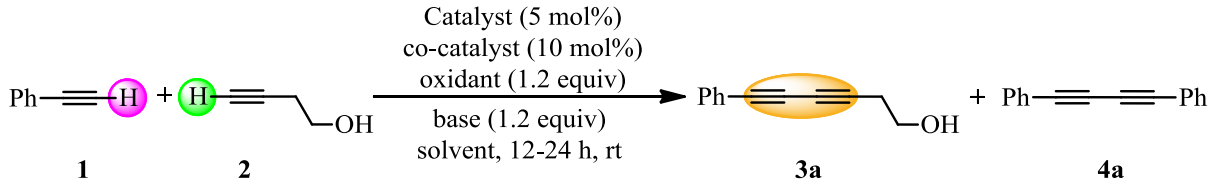


Figure 1. Literature report and present work

Gold-catalyzed redox process has emerged as a great alternative for traditional cross-coupling reactions. Recently, Shi et al. significantly demonstrated the Au/phen/$PhI(OAc)_2$ oxidative cross-coupling of terminal alkynes, with high selectivity for cross-coupling. However, this process requires differences in electronic parameters of coupling partners.

Liu and Patil's groups individually reported the Au catalyzed cross-coupling of terminal alkynes with alkynyl hypervalent iodine (III). Though heteroselectivity is appreciable, availability and highly expensive alkynyl hypervalent iodine precursor constrained its practical application (Figure 1).

Our investigation began with cross-coupling of phenylacetylene with propargyl alcohol (Table 1). Surprisingly, our hypothesized reaction condition proceeded smoothly with high yields. However, inferior results were obtained in absence of Au(I) or Cu(I) (Table 1, entry 2-3). Toluene found to be the suitable solvent. No product formation was observed in presence of inorganic bases (entry 6-9) and among organic bases (Et_3N, pyridine, TMEDA, DIPA), DIPA has retained the high yields (entry 9-11). Further, screening of different co-catalyst modification such as CuCl, $CuCl_2$, and AgOTf, did not improve the yields (entry 12-14). Note that $AuCl_3$ or AuCl could not result in cross-coupling products (entry 15, 16).



Scheme 1. Synthesis of compound **3a**

Table 1. Optimization of catalytic system[a]

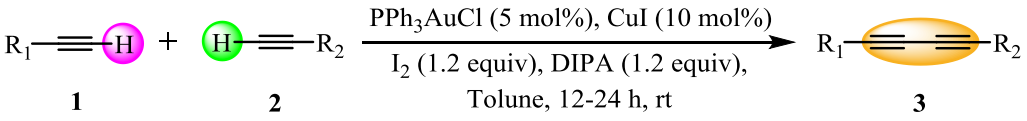
Entry	Reaction conditions	Solvent	Time	Yield(%)[b]	
				3a	**4a**
1	**PPh_3AuCl, CuI, I_2, DIPA**	**Toluene**	**12 h**	**86**	**5**
2	PPh_3AuCl, I_2, DIPA	Toluene	24 h	0	0
3	CuI, I_2, DIPA	Toluene	24 h	0	0

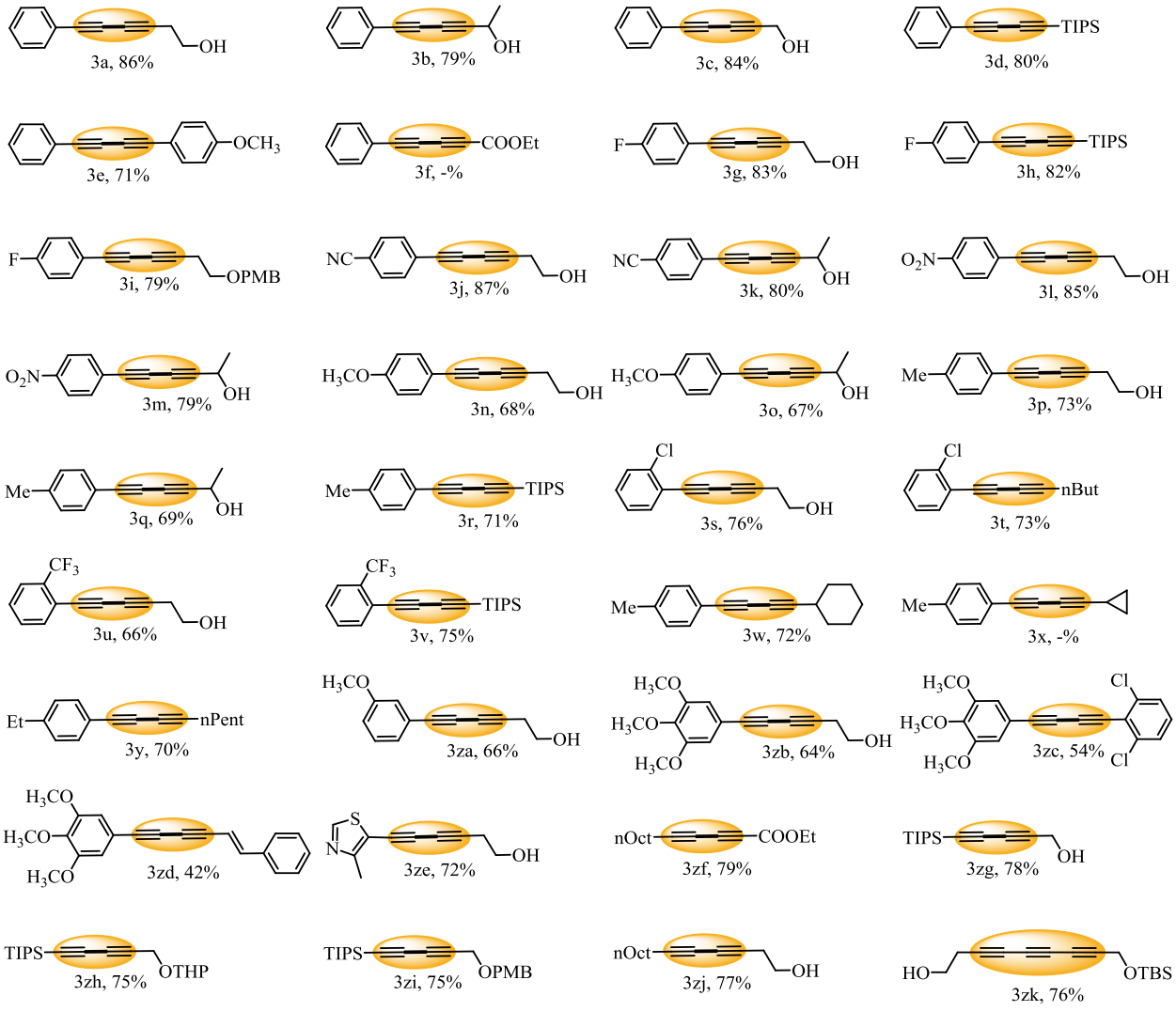
4	PPh_3AuCl, CuI, I_2, DIPA	THF	12 h	**72**	13
5	PPh_3AuCl, CuI, I_2, DIPA	Acetonitrile	12 h	**65**	15
6	PPh_3AuCl, CuI, I_2, Na_2CO_3	Toluene	24 h	0	0
7	PPh_3AuCl, CuI, I_2, K_2CO_3	Toluene	24 h	0	0
8	PPh_3AuCl, CuI, I_2, Cs_2CO_3	Toluene	24 h	0	0
9	PPh_3AuCl, CuI, I_2, Et_3N	Toluene	24 h	0	0
10	PPh_3AuCl, CuI, I_2, py.	Toluene	24 h	12	4
11	PPh_3AuCl, CuI, I_2, TMEDA	Toluene	12 h	**49**	10
12	PPh_3AuCl, CuCl, I_2, DIPA	Toluene	12 h	**53**	7
13	PPh_3AuCl, $CuCl_2$, I_2, DIPA	Toluene	12 h	**36**	9
14	PPh_3AuCl, AgOTf, I_2, DIPA	Toluene	24 h	0	0
15	$AuCl_3$, CuI, I_2, DIPA	Toluene	24 h	0	0
16	AuCl, CuI, I_2, DIPA	Toluene	24 h	0	0

[a]Reaction conditions: 1 (0.1 mmol), 2 (0.13 mmol), catalyst (5 mol%), co-catalyst (10 mol%), base (1.2 equiv), oxidant (1.2 equiv), and solvent (1.0 mL) at rt for 24-72 h. [b]Yield of Isolated product with 0.1 mmol scale.

Having optimized reaction conditions in hand, further, we explored the substrate scope of this novel protocol by changing the substitutions on both the coupling partners (Table 2). Initial attempt of one carbon elongation in propargylic alcohol, C-1 methyl group substitution with free-OH group, propargyl alcohol, TIPS-acetylene, and *p*-methoxy phenyl acetylene except ethylpropiolate resulted in high yields (71–86%) in cross-coupling with phenylacetylene **3a–3e**. For instance, *p*-substituted aromatic alkynes bearing electron-donating, electron-withdrawing, halo, or alkyl substituents with other coupling partner like homo propargyl alcohol, PMB protected homo propargyl alcohol, TIPS-acetylene, 2^o-butynol furnished the conjugated diynes **3g–r** in excellent yields (67–87%). Next, when *o*-substituted aromatic alkynes were used as the substrates, the reaction delivered **3s–v** in good to excellent yields (66–76%) irrespective of the electronic bias of the corresponding terminal alkynes. Further, *p*-alkyl (methyl, ethyl) substituted aromatic alkynes crosscoupling with aliphatic alkynes i.e cyclic or acyclic except cyclopropylacetylene to obtain corresponding conjugated diynes **3w–y** in good yields (70–72%). Notably in the case of *m*-methoxy and 1,3,5-trimethoxy substituted aromatic alkynes were used as the substrates, the heterocoupling products **3za-zd** yielded moderately (42–66%).

Table 2. Substrate scope of Au(I)/Cu(I)- catalyzed intermolecular Glaser-Hay coupling[a,b]





[a]Reaction conditions: **1** (0.1 mmol), **2** (0.13 mmol), PPh_3AuCl (5 mol%), CuI (10 mol%), DIPA (1.2 equiv), I_2 oxidant (1.2 equiv), and solvent (2.0 mL) at rt for 12 h. [b]Yield of Isolated product with 0.2 mmol scale.

The scope of the reaction was further extended to heteroaromatic alkyne, such as thiazole yielded corresponding diacetylene **3ze** in good yield (72%). The practicability of the method was further

tested with both the aliphatic terminal alkynes as substrates. Intrestingly, furnishing the crosscoupled products **3zf–zi** in excellent yields (75–79%).

(3*E*,5*Z*)-3,5-tetradecadienoic acid (Megatomic acid), the sex attractant of the black carpet beetle, following the customary procedure of the Glaser-Hay cross coupling reaction of 1-decyne and 3-butyn-1-ol in the presence of Au(I)/Cu(I) affording 3,5-tetradecadiyn-1-ol **3zj** in 77% yield.

Crosscoupling of propargyl alcohol with diyne by synergistic Gold and Copper dual catalysis for cross-coupling of terminal alkynes protocol with Au(I) and Cu(I) in presence of iodine and DIPA in toluene at room temperature for 12 h to afford triyne **3zk** in 76% yield.

A gram-scale synthesis was also performed to verify the practical synthesis using this method, the gram-scale synthesis of **3c** was successfully achieved in 79 % yield.

Conclusion:

In summary, we present a highly synergistic Au(I)/Cu(I) dual catalytic system for Glaser-Hay cross-coupling with terminal alkynes for the synthesis of a wide range of unsymmetrical conjugated diynes. This highly efficient protocol enabling crosscoupling of terminal acetylenes without prefuntionalization or excess amount of one coupling partner. This novel method has demonstrated for broad substrate scope and a wide range of functional group tolerance. Detailed mechanistic investigation and further applications in organic synthesis are in progress.

Section C: This section describes application to Synergistic Gold and Copper dual catalysis for Intramolecular Glaser-Hay coupling.

Macrocycles are important structural moieties in medicinal and biological research, and efficient methods for macrocyclization are always in high demand. With the unique conformation having six carbon atoms in a linear geometry, the cyclic conjugated diynes present greater synthetic challenges and have been much less explored. Therefore, application of these unique macrocycles in biological studies is largely unexplored. Metal mediated oxidative dimerization of terminal alkynes with stoichiometric amount of copper was developed by Glaser about 150 years ago. Modified reactions such as Glaser-Hay and Cadiot-Chodkiewicz coupling reactions were devloped later to prepare unsymmetrical conjugated diynes. Cadiot-Chodkiewicz coupling though powerful, often suffers from poor selectivity and formation of homo-coupled byproducts.

To specifically address the problems related to optimizing chemoselectivity in homo-coupling of alkynes, either of the terminal alkynes should be immobilized on a solid support or should be converted to a haloalkyne under high dilution conditions. Less is known about the Glaser-Hay coupling for macrolactonization, although recent studies by Collins et al. disclosed a novel strategy employing copper catalysis and high concentrations for the synthesis of macrocycles using a "phase separation strategy".

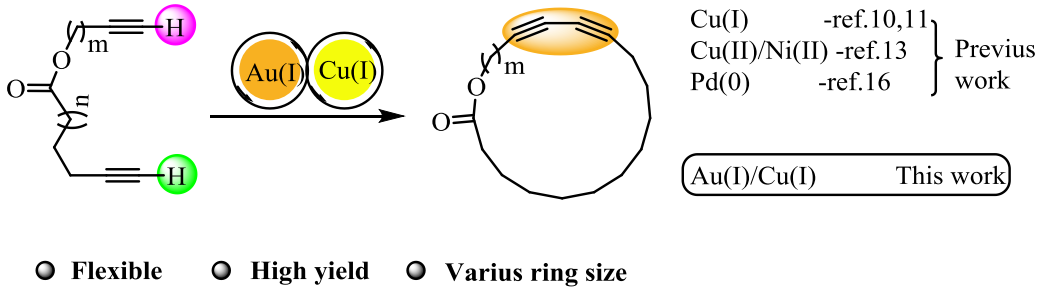
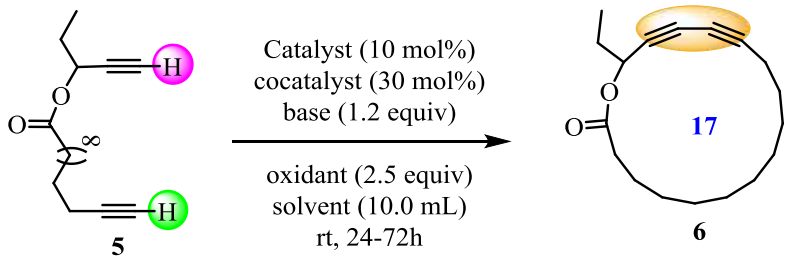


Figure 2. Synergistic Gold and Copper dual catalysis for the intramolecular Glaser-Hay coupling

We disclose herein, the use of gold-copper catalyst system to effect direct macrocyclization (Figure 2). So far very few examples are reported to achieve intermolecular Glaser-Hay coupling reaction with gold complexes. One of the alkynes behaves as an immobilized haloalkyne to form heterodiynes in excellent yield under homogenous conditions. We envisioned that gold catalyst could form complex with one of the alkynes and behave like a haloalkyne or immobilized alkyne leading to improve chemoselectivity via intramolecular Glaser-Hay coupling for macrocyclization in an unprecedented manner. However, to date, gold-catalyzed intramolecular Glaser-Hay coupling was not utilized to synthesize diyne containing macrolactones.

Our investigations began with the macrocyclization of model substrate ester **5**, via intramolecular Glaser-Hay coupling of terminal alkynes (Scheme 2). Our initial screening results concerning different metal catalysts and reagents are listed in Table 1. Treatment of ester **5** under standard intermolecular Glaser-Hay coupling reaction conditions for macrocyclization (CuCl/TMEDA), led to low yield of the required product along with products resulting from polymerization (Table 1, entry 1). Similarly, Pd-catalyzed reaction also proceeded with low yield although complete consumption of starting material (entry 3) was observed. Macrocyclization under Shi's

conditions afforded trace amount of lactone **6** accompanied with decomposition of the starting material (entry 4 and 5). When the ester was treated with the conditions reported by Corma et al., it did not afford the required product (entry 6). When we employed catalytic amount of Au(I)/Cu(I) catalyst in combination for the macrocyclization a yield of 49% was realized (entry 7). To optimize these reaction conditions, different Au(I) catalysts were screened. Increase of reaction yield as well as the catalyst stability was observed with dppm$(AuBr)_2$ (entry 7). When the dppm$(AuBr)_2$ was replaced with PPh_3AuCl catalyst, gratifying increase of the yield (68%) was observed (entry 8). Next, different bases were screened.



Scheme 2. Synthesis of compound **6**

Table 3. Optimization of catalytic system[a]

Entry	Reaction conditions	Solvent	time	Yield(%)[b]
1	CuCl, TMEDA, O_2	Toluene	2 d	19
2	CuI, I_2, DIPA	Toluene	2 d	18
3	$Pd(PPh_3)_2Cl_2$, CuI, I_2, DIPA	THF	2 d	32
4	PPh_3AuCl, BAIB, Phen	Acetonitrile	2 d	trace
5	dppm$(AuBr)_2$, BAIB, Phen	Acetonitrile	2 d	trace
6	$AuPPh_3NTf_2$, selectofluor, Na_2CO_3	Acetonitrile	1 d	0
7	dppm$(AuBr)_2$, CuI, I_2, DIPA	Acetonitrile	2 d	49
8	PPh_3AuCl, CuI, I_2, DIPA	Acetonitrile	2 d	68
9	PPh_3AuCl, CuI, I_2, Na_2CO_3	Acetonitrile	3 d	0
10	PPh_3AuCl, CuI, I_2, K_2CO_3	Acetonitrile	3 d	0
11	PPh_3AuCl, CuI, I_2, Cs_2CO_3	Acetonitrile	3 d	0
12	PPh_3AuCl, CuI, I_2, Et_3N	Acetonitrile	3 d	<20
13	PPh_3AuCl, CuI, I_2, py.	Acetonitrile	3 d	<20

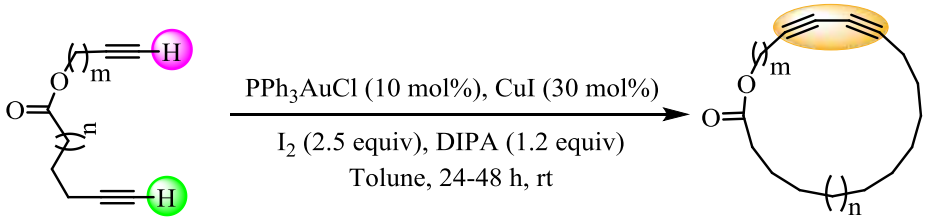
14	PPh_3AuCl, CuI, I_2, TMEDA	THF	2 d	45
15	PPh_3AuCl, CuI, I_2, DIPA	THF	2 d	71
16	**PPh_3AuCl, CuI, I_2, DIPA**	**Toluene**	**2 d**	**86**
17	PPh_3AuCl, CuCl, I_2, DIPA	Toluene	2 d	66
18	PPh_3AuCl, $CuCl_2$, I_2, DIPA	Toluene	2 d	39
19	PPh_3AuCl, CuI, DIPA/O_2	Toluene	3 d	trace
20	PPh_3AuCl, AgOTf, I_2, DIPA	Toluene	1 d	trace
21	$AuCl_3$, CuI, I_2, DIPA	Toluene	1.5 d	trace
22[c]	PPh_3AuCl, CuI, I_2, DIPA	Toluene	2 d	79

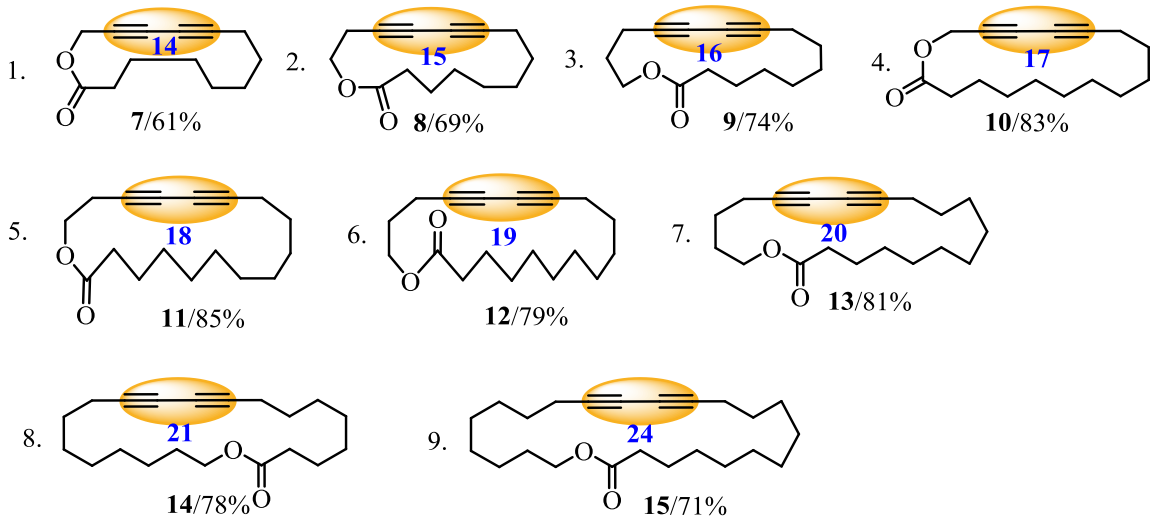
[a]Reaction conditions: **5** (0.1 mmol), catalyst (10 mol%), cocatalyst (30 mol%), base (1.2 equiv), oxidant (2.5 equiv), and solvent (10.0 mL) at rt for 24-72 h. [b]Yield of Isolated product with 0.1 mmol scale. [c]The reaction was carried out on one gram scale.

No product was formed with inorganic bases (entry 9-11) and among organic bases (Et_3N, pyridine, TMEDA, DIPA), DIPA was found to be the best base leading too good yields (entry 12-15). An investigation of the impact of solvents showed that toluene worked best for the smooth conversion of diynes to corresponding macrolactones in the presence of 10 mol% PPh_3AuCl (10 mol%), CuI (30 mol%), I_2 (2.5 equiv.) and DIPA (1.2 equiv.), producing **6** in 86% yield (entry 16). Screening of different copper catalysts revealed low yield of the macrocyclization obtained with other co-catalysts such as CuCl, $CuCl_2$ and AgOTf. When Au(III) catalyst was used in place of Au(I) catalyst, a trace amount of **6** was observed (entry 21). The above optimized condition was also used for gram scale synthesis to afford compound **6** in 79% yield (entry 22).

In an effort to evaluate the generality of the optimized conditions, the macrocyclization of other diynes with different ring size was performed (Table 4). Change in the macrolactone ring sizes from 14- to 24-membered ring (**7**-**15**), did not significantly change the reaction yield except 14- and 15-membered ring formation were found in moderate yield along with oligomerized products in 11% and 7%, respectively (Table 4, entry 1 and 2). During the investigation of the macrocyclization of larger ring macrolactones, it was found that macrolactones having ring sizes 16-20 at high concentrations afforded the respective macrolactones in excellent yield. For 21- and 24-membered macrolactones, the yield was 78% and 71%, respectively.

Table 4. Substrate scope of Au(I)/Cu(I)- intramolecular Glaser-Hay coupling[a]





[a]The reaction was carried out on a 0.05 mmol scale.

While the precise reaction mechanism is not yet known, a plausible mechanism is shown in Figure 3. It is postulated that homogenous gold catalysts in situ generates organogold species which behaves like immobilized alkyne leading not only to the heterocoupling under high concentrations (0.01 M) but also enhances the yield of the macrolactone formation. The pathway is proposed as follows: The alkyne in presences of base and gold(I) catalyst forms the gold acetylide[41] complex and simultaneously other alkyne forms copper acetylide. The oxidative transmetalation of the organocopper species to Au^{III} in presence of molecular iodine lead to intermediate **IV**. Diisopropyl amine assisted reductive elimination of Au^{III} bis-acetylide complex yields the product with removal of Au^{I} species and continues the next catalytic cycle (Figure 3).

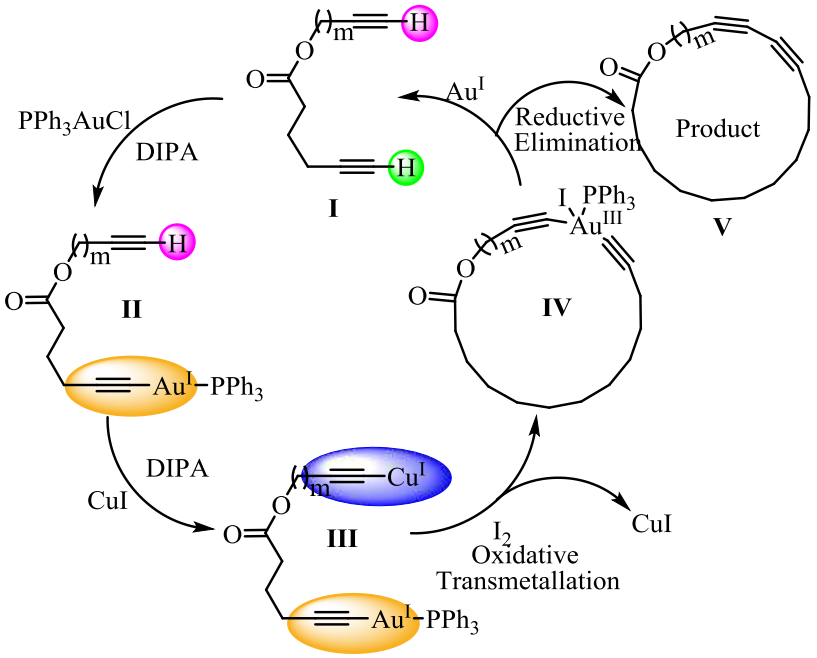


Figure 3. Possible mechanistic pathway

Conclusion:

In summary, we have developed a highly synergistic Au(I)/Cu(I) dual catalytic system for intramolecular Glaser-Hay coupling with linear terminal alkynes for the synthesis of macrolactones. The gold/copper conditions also can be utilized to promote macrocyclization of a wide range of macrocycles with varying ring sizes in excellent yields. The detailed mechanistic investigation and further applications in organic synthesis are in progress.

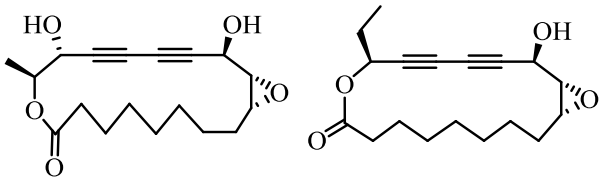
CHAPTER II:

Section A: This section deals with the brief introduction and previous synthetic approaches of Ivorenolides.

Section B: This section describes the total synthesis of Ivorenolide B.

Macrocycles are widespread structural motifs present in natural products, pharmaceuticals, material science compositions, and have profound importance in supramolecular chemistry. Among these, 1,3-butadiynes or di-acetylenic scaffolds occur widely and to date, over one thousand naturally occurring polynes were isolated and were found to display antibacterial, anti-cancer, anti-HIV, antifungal properties. Further, conjugated diynes play an important role in the

properties of many functional materials, such as nonlinear plastics, fibers with high density and strength, and liquid crystals. A new class of 1,3-butadiyne macrolides ivorenolide A and B (Figure 4) exhibiting immunosuppressant activities was isolated from the species *Khaya ivorenis*. Immunosuppressive therapy usually has to follow surgery to ensure the success of organ transplantation and also for treatment of autoimmune diseases, including rheumatoid arthritis, systemic lupus erythematosus (SLE), psoriasis, and multiple sclerosis. Synthesis of conjugated diynes especially unsymmetrical diynes, depicted below is of clinical relevance.

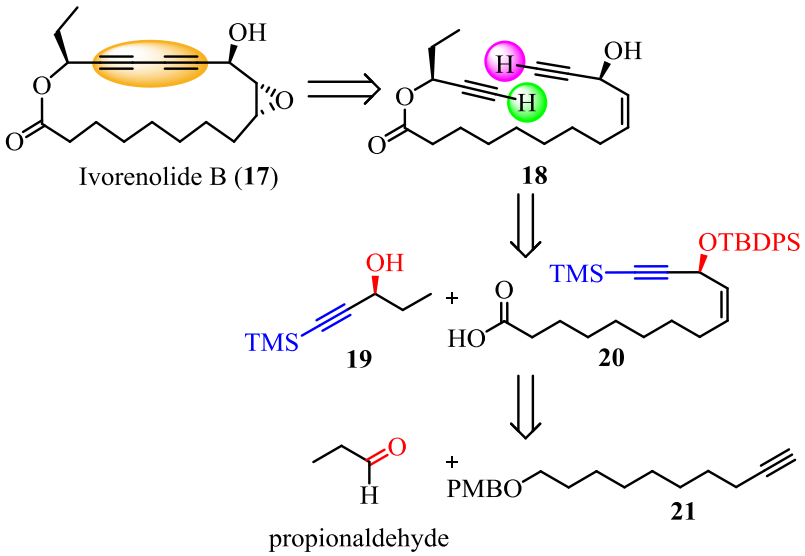


Ivorenolide A (**16**) Ivorenolide B (**17**)

Figure 4. Structures of Ivorenolide A (**16**) and B (**17**)

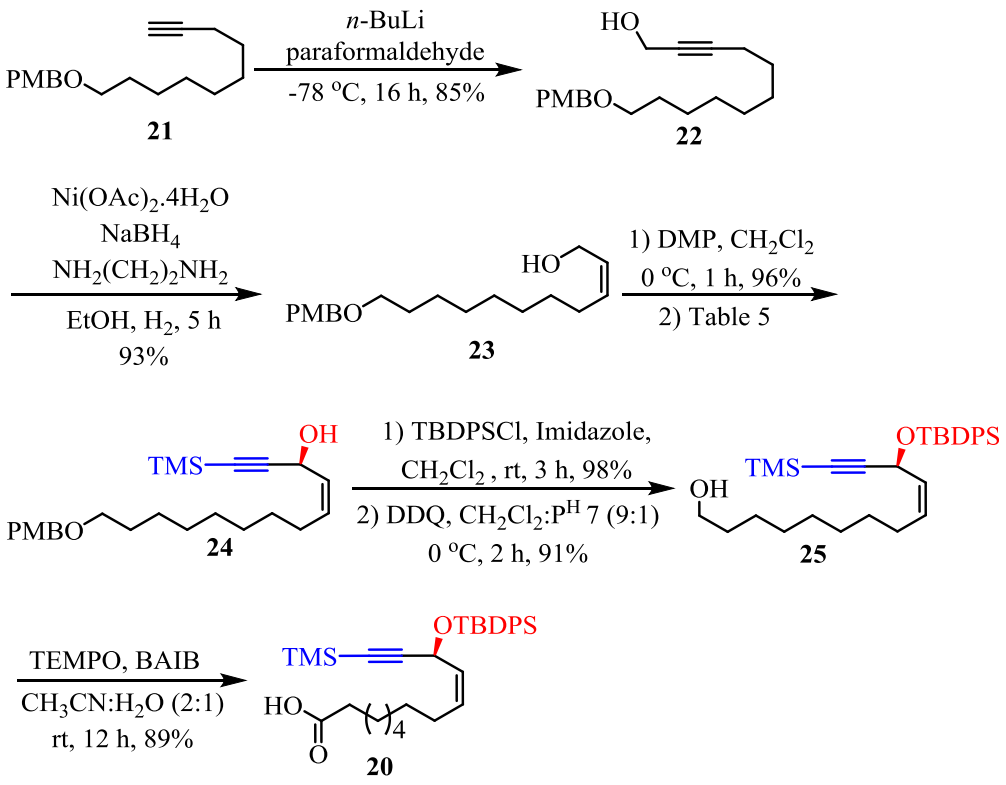
To demonstrate the utility of the novel macrocyclization, synthesis of the 17-membered macrolide ivorenolide B was undertaken. Yue et al. and our group independently achieved the total synthesis of *ent*-ivorenolide A (**16**) and ivorenolide A (**16**), respectively, utilizing alkyne-alkyne cross-coupling followed by macrolactonization. Collins et al. recently reported the formal total synthesis of ivorenolide A by following macrocyclization strategies under phase separation conditions using continuous flow. Further, Yue et al. reported the first total synthesis of ivorenolide B (**17**), which was achieved through esterification followed by RCM. Furstner et al. reported the second synthesis of ivorenolide B using ring-closing alkyne metathesis (RCAM) based macrocyclization, which involved highly unstable tetrayne precursors.

In our current work, the development of a Au(I)/Cu(I)-catalyzed macrocyclization for the synthesis of ivorenolide B was envisaged through intramolecular Glaser-Hay coupling which disconnects the molecule framework at conjugated 1,3-diyne bond leading to terminal alkynes ester **18** as an advanced intermediate for the formation of 17-membered macrolactone. The linear ester fragment **18** could be prepared by coupling of alcohol **19** and acid **20** under Yamaguchi conditions. Syntheses of both fragments were anticipated following a reliable direct catalytic asymmetric alkynylation strategy starting from PMB-protected 9-decyn-1-ol **21** and propionaldehyde, respectively (Scheme 3).



Scheme 3. Retrosynthetic analysis of Ivorenolide B

The synthesis of carboxylic alkynyl synthons **20** commenced from PMB-protected 9-decyn-1-ol. Hydroxymethylation followed by *Z*-selective partial reduction of the acetylene was performed to furnish *Z*-alcohol **23** in 79% yield over two steps. Oxidation of allylic alcohol with Dess-Martin-periodinane (DMP) furnished the α,β-unsaturated aldehyde, which was subjected to zinc-ProPhenol-catalyzed alkyne addition to provide the propargyl alcohol **24** in 94% enantiomeric excess and with 91% yield. At this juncture, in anticipation for a better result, the substrate **24** (for results, see Table 5) was prepared by BINOL-mediated alkyne addition, oxidation followed by Noyori asymmetric hydrogenation and enzymatic kinetic resolution. The secondary hydroxyl group present in compound **24** was obtained through zinc-ProPhenol catalyzed addition, was protected as its TBDPS ether and treated with DDQ in CH_2Cl_2 (pH 7) to afford **25** in 89% yield over two steps. The primary alcohol **25** was oxidized to acid under TEMPO/BAIB in CH_3CN:H_2O (2:1) to obtain acid **20** in 89% yield (Scheme 4). With acid **20** in hand, the alkynylation of propionaldehyde was accomplished under Trost's conditions using zinc-ProPhenol as the chiral ligand and adding trimethylsilylacetylene (TMSA) slowly over 1 h at 0 ^oC to furnish alcohol **19** in 70% yield with 89% ee.

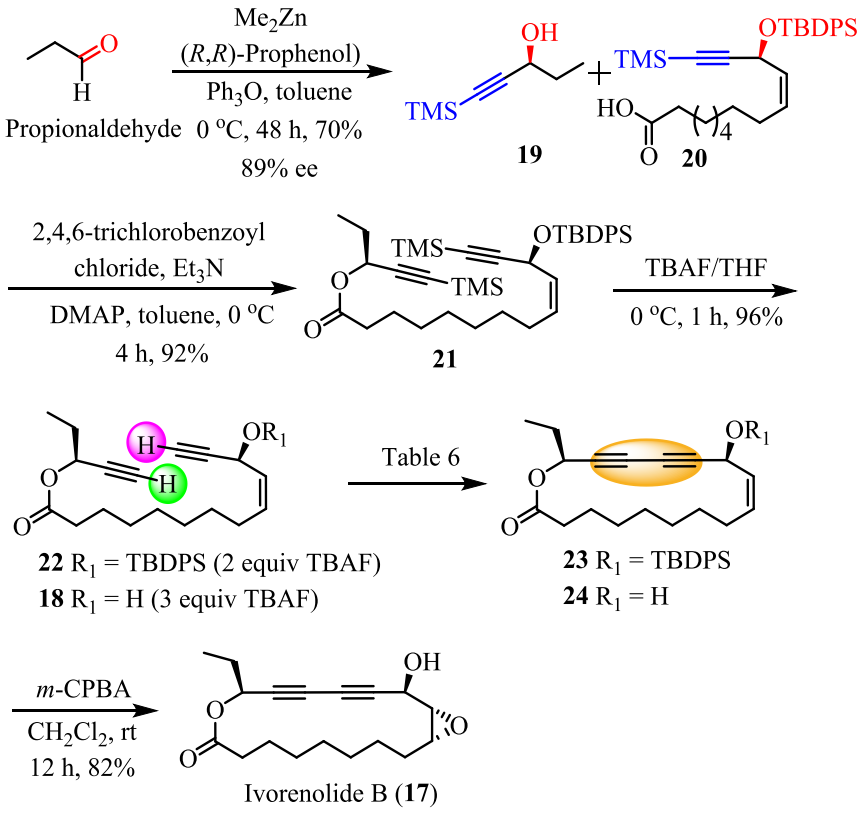


Scheme 4. Synthesis of fragment **20**

Table 5.

Entry	Reaction conditions	ee	Yield (%)
1	Me_2Zn, (*R*,*R*)-Prophenol, $Ph_3P{=}O$	94	91
2	Et_2Zn, (*R*)-Binol, $Ti(OiPr)_4$	70	79
3	Noyori asymmetric reduction	91	82
4	Novozym Enzymatic resolution	93	39

Union of the alcohol fragment with the acid fragment was achieved smoothly under Yamaguchi conditions to furnish ester **21** in 92% yield. Deprotection of all silyl groups using TBAF in THF afforded **22** in 96% yield. The stage was set to perform the macrocyclization using Au(I)/Cu(I) in presence of iodine and DIPA in toluene. When intramolecular Glaser-Hay coupling was tried with the linear terminal alkynes with the secondary hydroxyl group protected as its TBDPS ether, macrocyclization occurred and **23** was obtained in 67% yield after two days (see Table 6).



Scheme 5. Total Synthesis of Ivorenolide B

Table 6.

R_1	Reaction conditions	time (d)	Yield (%)
TBDPS	$AuCl(Ph_3P)/CuI/I_2/DIPA$	2	67
-H	$AuCl(Ph_3P)/CuI/I_2/DIPA$	1.5	81
-H	$Pd(PPh_3)_2Cl_2/CuI/I_2/DIPA$	2	36
-H	CuCl, TMEDA, O_2	2	15

Speculating that the presence of a bulky TBDPS group might be responsible for the low yield, the TBDPS ether linkage was cleaved and the macrocyclization precursor **18** was subjected to intramolecular Glaser-Hay coupling under identical conditions to afford the desired macrocycle **24** in 81% yield. The same reaction was also tried under Sonogashira type coupling and general Glaser-Hay coupling conditions which ended up with desired product in low yield (Table 6). Subsequent epoxidation with *m*-CPBA was highly regio- and stereoselective to furnish ivorenolide B (**17**) in 82% yield as a single isomer (Scheme 5).

Conclusion:

In summary, the versatility of the protocol was demonstrated in the rapid asymmetric total synthesis of ivorenolide B. All analytical and spectral data of the synthetic ivorenolide B (**17**) were in full agreement with those of the natural product reported in the literature.

Chapter III:

Section A: This section deals with the brief introduction and previous synthetic approaches of vernoniynes.

Section B: This section describes the total synthesis of 1′,8′-Dihydroxy-3,4-dihydrovernoniyne.

Recently, Biavatti and co-workers isolated eight polyacetylene containing butyrolactone natural products **25-32**, seven of which are new, from the leaves of *Vernoniascorpioides* (*Asteraceae*) (Figure 5). This herb is used in folk medicine for the treatment of several skin diseases, such as allergies, skin parasites, irritation, chronic skin injuries (ulcers) and itching. Their structures were established by 1D and 2D NMR spectroscopy and MS analysis.

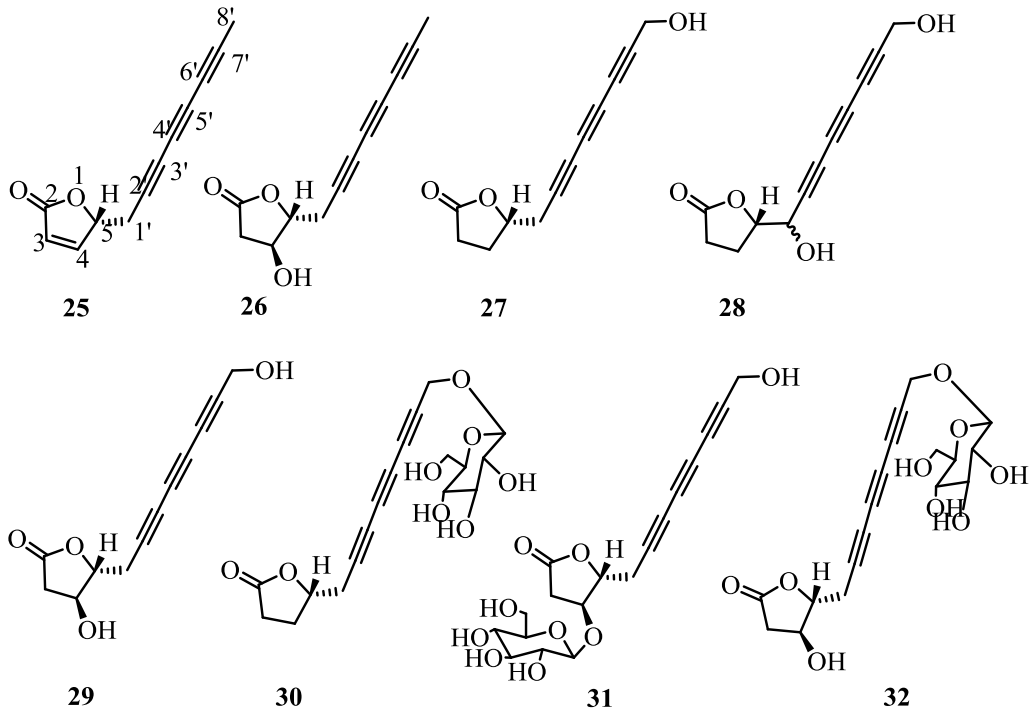
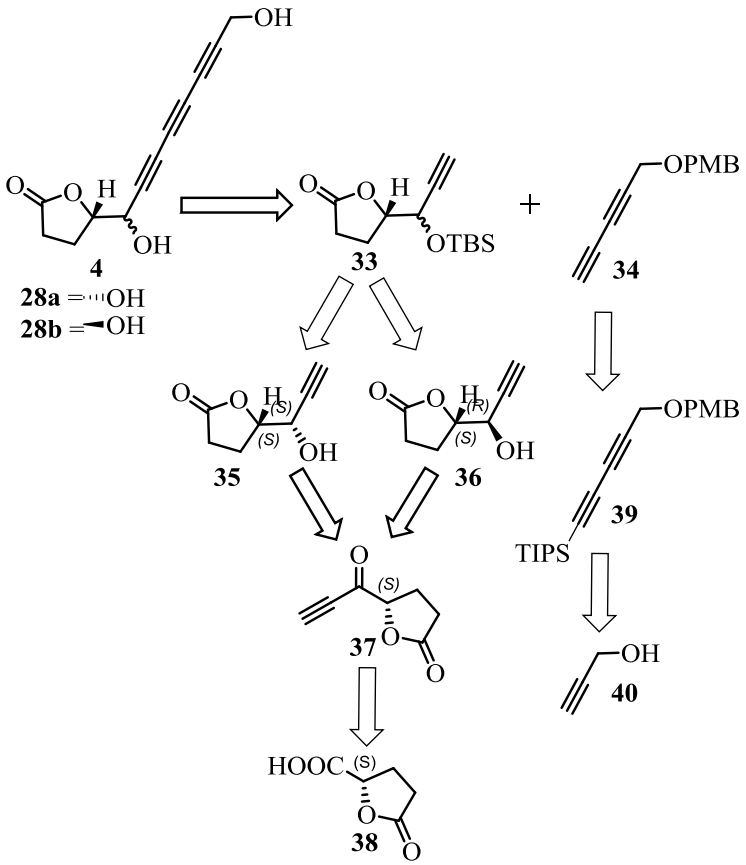


Figure 5. Structures of polyacetylenes **25–32**

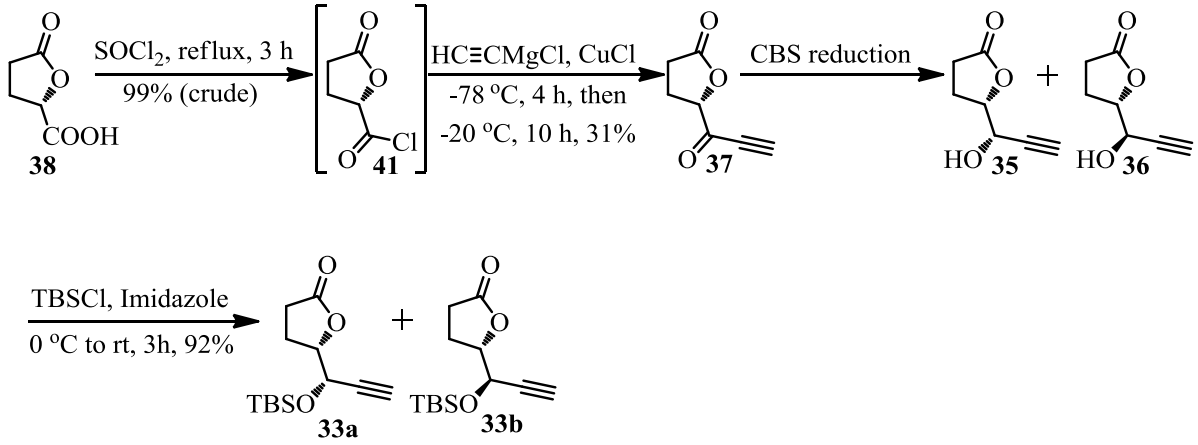
We recently accomplished the first asymmetric total synthesis of triyne containing natural product (4*S*,5*R*)-4,8-dihydroxy-3,4-dihydrovernoniyne (**29**) and revision of its absolute stereochemistry **29a**. In continuation of our efforts, we report herein, the first asymmetric concise total synthesis of two isomers of proposed structures of 1′,8′-Dihydroxy-3,4-dihydrovernoniyne (**28a**, **28b**).

The retrosynthetic route for the synthesis of 1′,8′-Dihydroxy-3,4-dihydrovernoniyne **28** is illustrated in Scheme 6. We envisioned that a convergent strategy based on the coupling of functionalized alkyne in **33** and diyne **34** by recently developed synergistic gold and copper dual catalysis for cross-coupling of terminal alkynes protocol. The functionalized alkyne in **33** could be synthesized from the lactone-carboxylic acid **38**, which was readily derived from *L*-glutamic acid following the well-established literature procedure. Similarly, the diyne **34** can be obtained from propargyl alcohol **40** and TIPS acetylene by recently developed synergistic Gold and Copper dual catalysis for cross-coupling of terminal alkynes protocol.



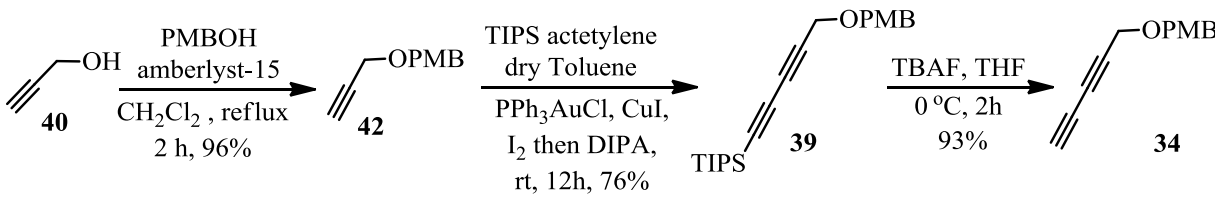
Scheme 6. Retrosynthetic analysis of 1′,8′-Dihydroxy-3,4-dihydrovernoniyne (**28**)

The new route (Scheme 7) started with the lactone-carboxylic acid **38**, which was readily derived from *L*-glutamic acid following the well-established literature procedure. Treatment with $SOCl_2$ at reflux for 3 h gave the crude acid chloride **41** in 99% yield. Subsequent addition of an acetylene moiety to **41** under the simplest conditions (HC≡CMgCl, CuCl, −78 °C, 4 h, then -20 °C, 10h), to afford the desired product **37** in 31% yield. The ketone **37** was reduced to corresponding alcohols **35** and **36** under CBS (Corey–Bakshi–Shibata) reduction (BH_3, (*R*)- or (*S*)-2-methyl-CBS-oxazaborolidine, 0 °C) gave better total yields (92% or 95% with the (*R*)- or (*S*)-oxazaborolidine catalyst, respectively). The alkynol **35** and **36** was treated with TBSCl and imidazole in CH_2Cl_2 to furnish silyl ether **33a** and **33b** in 92% yield.



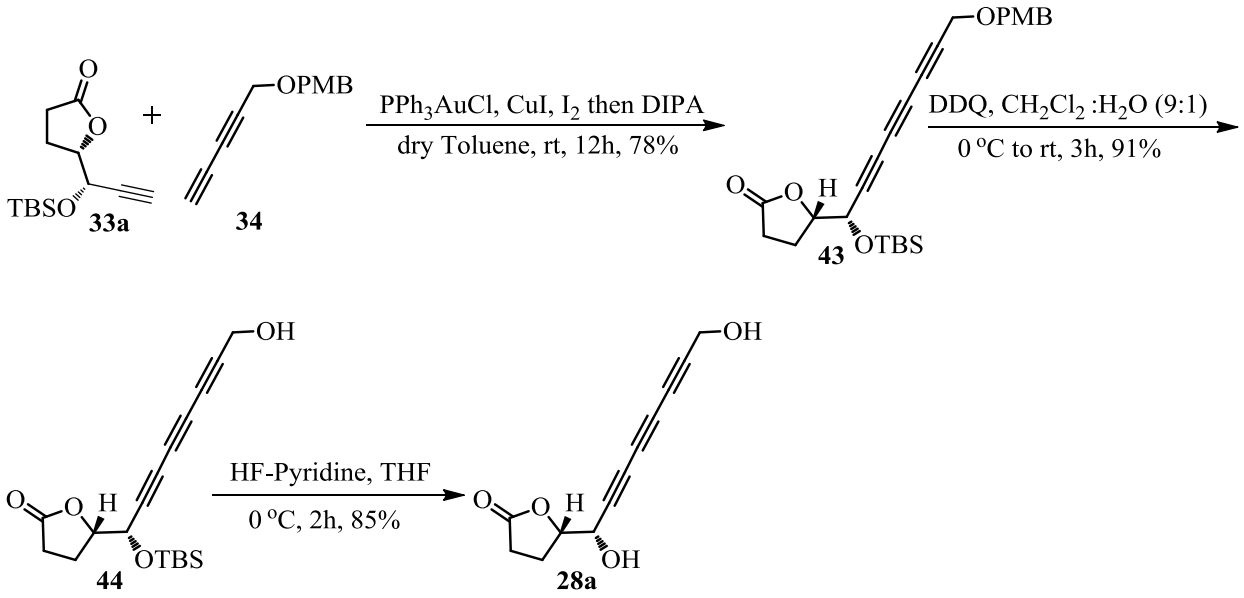
Scheme 7. Synthesis of alkyne fragment **33**

As outlined in Scheme 8, the synthesis of the second fragment **34** started with the transformation of commercially available propargyl alcohol **40** into the PMB ether following a mild one-step heterogenous protocol afforded PMB ether **42** in 96% yield. Coupling of alkyne **42** with TIPS-acetylene under recently developed synergistic gold and copper dual catalysis for cross-coupling of terminal alkynes protocol provided the cross-coupling product **39** in 76% yield. Selective deprotection of the *C*-silyl group of **39** using TBAF provided diyne **34** in 93% yield (Scheme 8).



Scheme 8. Synthesis of diyne fragment **34**

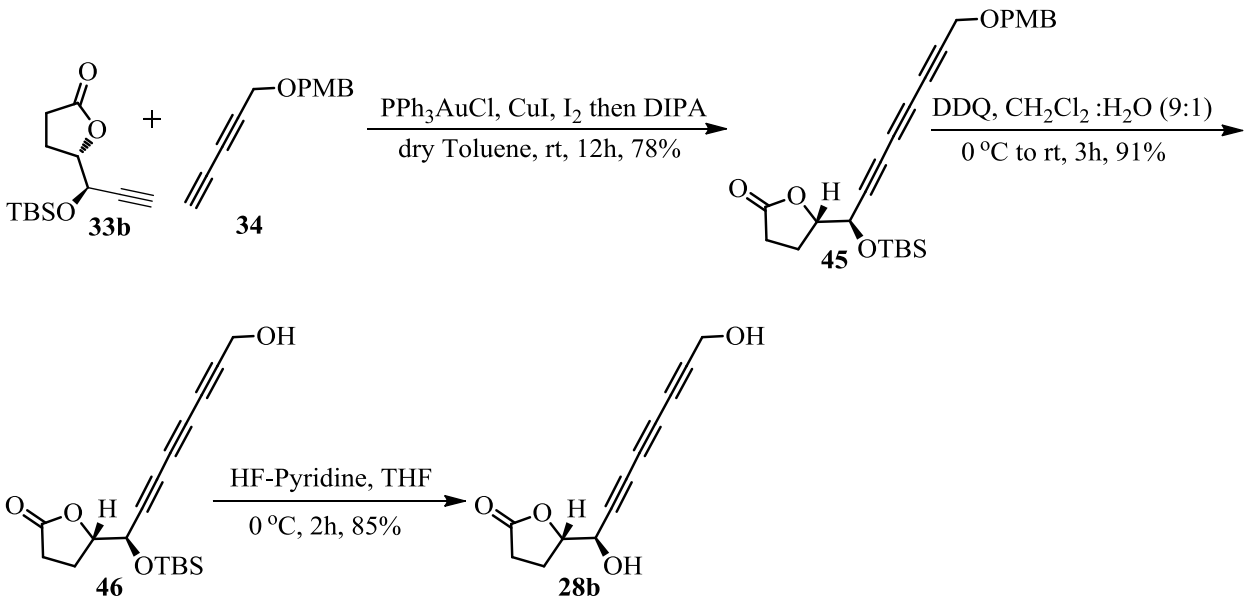
Having secured both the coupling partners **33a/33b** and **34**, crosscoupling of the alkyne **33a** with diyne **34** under recently developed synergistic gold and copper dual catalysis for cross-coupling of terminal alkynes protocol provided the triyne **43** in 78% yield (Scheme 9).



Scheme 9. Synthesis of 1′,8′-Dihydroxy-3,4-dihydrovernoniyne **28a**

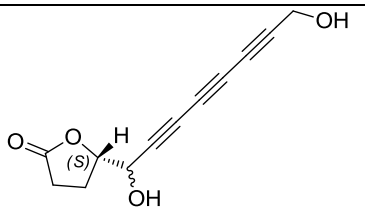
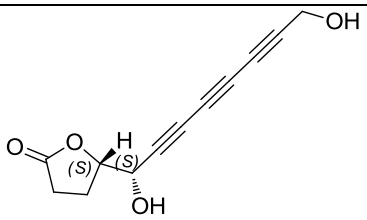
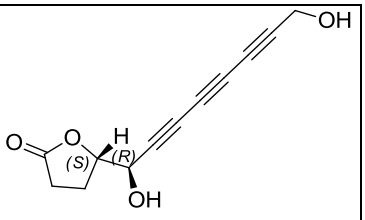
The PMB group in compound **43** was selectively deprotected with DDQ under standard reaction conditions to furnish the primary alcohol **44** in 91% yield. Deprotection of the TBS ether in **44** with HF in pyridine at 0 °C provided (4*S*,5*R*)-4,8-dihydroxy-3,4-dihydrovernoniyne **28a** in 85% yield.

After achieveing the synthesis of **28a**, total syntheis of **28b** was initiated. For the same, crosscoupling of the alkyne **33b** with diyne **34** under recently developed synergistic gold and copper dual catalysis provided the triyne **43** in 78% yield. The PMB group in compound **45** was selectively deprotected with DDQ under standard reaction conditions to furnish the primary alcohol **46** in 91% yield. Deprotection of the TBS ether in **46** with HF in pyridine at 0 °C provided (4*S*,5*R*)-4,8-dihydroxy-3,4-dihydrovernoniyne **28b** in 85% yield (Scheme 10).



Scheme 10. Synthesis of 1′,8′-Dihydroxy-3,4-dihydrovernoniyne **28b**

The ^{1}H NMR and ^{13}C NMR data (as no optical rotation value was given in the literature) of the synthesized compounds **28a** and **28b** were compared with the natural product which was reported earlier by Biavatti et al. The two synthetic products **28a** and **28b** had identical spectra to each other, but showed significant deviation from spectrum of the natural product, with no significant influence of the configuration at the C1′ stereocenter.

Pcx						
	δ^{1}H (mult., J Hz)	δ^{13}C	δ^{1}H (mult., J Hz)	δ^{13}C	δ^{1}H (mult., J Hz)	δ^{13}C
2		176.5		176.5		176.9
3	2.56 m, 2.51 m	27.6	2.70-2.53 (m, 2H)	28.0	2.70 m, 2.53 m	27.99
4	2.31 m, 2.19 m	22.8	2.37 m, 2.23 m,	23.2	2.38-2.20 (m, 2H)	21.9
5	4.58 m	80.5	4.61 m	80.9	4.71 d	80.8
1′	4.54 m	63.4	4.56 m	64.8	4.65 dt	64.5
2′		76.8		77.2		77.5
3′		69.4		69.2		69.1

4′		62.5		**75.3**		**74.9**
5′		59.7				
6′		68.6		70.9		71.1
7′		78.1		78.4		78.4
8′	4.22 s	49.7	4.36 s	51.3	4.35 s	51.3

Table 7: Comparison of ^{1}H and ^{13}C NMR of Natural Product with Synthetic **28a** and **28b** in $CDCl_3$ (400 MHz)

Conclusion:

In summary, we have achieved the first asymmetric total synthesis of two isomers of the proposed structures for 1′,8′-Dihydroxy-3,4-dihydrovernoniyne. The key steps in the synthesis involved our own developed protocol for the construction of conjugated 1,3 diyne system by synergistic Gold and Copper dual catalysis for cross-coupling of terminal alkynes. The discrepancies between the spectroscopic data of the synthetic isomers of 1′,8′-Dihydroxy-3,4-dihydrovernoniyne and the isolated natural product, suggests that the structure proposed for the natural product needs revision.