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Novel Synthetic Approach Toward (±)-β-Cuparenone via Palladium-Catalyzed Tandem Heck Cyclization of 1-Bromo-5-methyl-1-aryl-hexa-1,5-dien-3-ol Derivatives

Devalina Ray and Jayanta K. Ray*

Department of Chemistry, Indian Institute of Technology, Kharagpur 721302, India

jkray@chem.iitkgp.ernet.in

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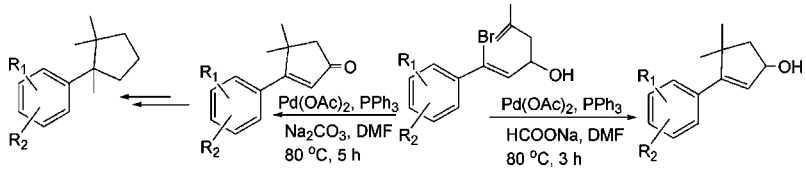
ABSTRACT



A novel and convenient synthetic route toward (±)-β-cuparenone and many other sesquiterpene natural product precursors has been developed via palladium-catalyzed tandem Heck cyclization of 1-bromo-5-methyl-1-aryl-hexa-1,5-dien-3-ols.

As part of our ongoing interest in palladium-catalyzed Heck reactions,[1] we were interested in developing a new methodology and extending it to the synthesis of some of the sesquiterpene natural product precursors. A large number of multistep methods have been developed for the synthesis of (±)-α- and (±)-β-cuparenone, (±)-herbertene, etc., where the synthetic approaches are lengthy, hazardous, or low yielding.[2−6] A single-step synthesis of (±)-α-cuparenone has also been reported with an overall yield of 18% of the desired product.[7] In contemplating ways to reduce the steps as well as to keep the yield moderate, we found that one of the potential solutions would be to explore the option of synthesizing the precursors through palladium-catalyzed intramolecular Heck reactions which could be converted to the desired natural product, i.e., (±)-β-cuparenone, in one step.[8] Other natural products such as (±)-cuparene, (±)-herbertene, (±)-α-herbertenol, and (±)-β-herbertenol can be synthesized in two or three steps from our precursors. In contrast to other methodologies aiming at a similar goal,[9] our approximation leads to a simple, efficient, and good yielding route. Our urge to develop a practical and good yielding technique with less steps rendered the objective of investigating an unusual palladium-catalyzed tandem Heck cyclization.

In this context, we wish to highlight the formation of the gem dimethyl cyclopentenone moiety from 1-bromo-5-

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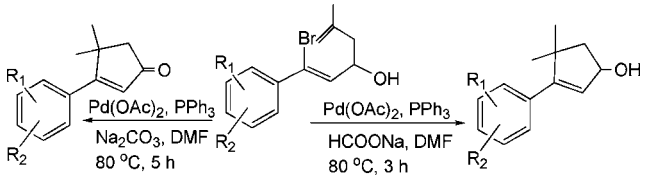
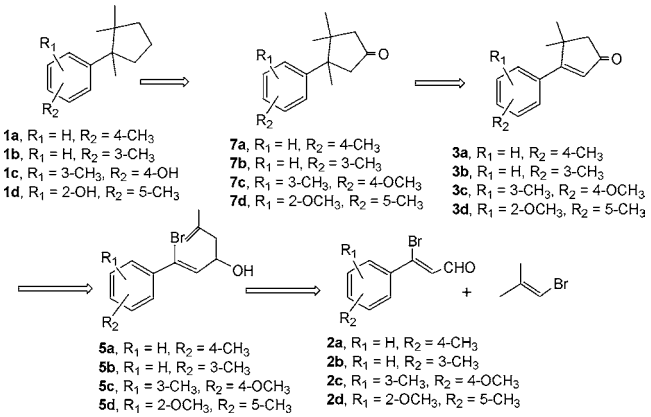
methyl-1-aryl-hexa-1,5-dien-3-ol using palladium-catalyzed Heck reaction conditions.

Scheme 1



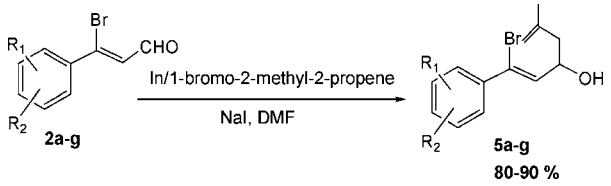
Well aware of the possibilities offered by this reaction, we utilized the method to obtain two different products from a common starting material by varying the reaction conditions (Schemes 1 and 2). Here lies the beauty of our methodology.

Scheme 2. Retrosynthetic Approach of **1a**−**d**



The convergent approach involved preparation of the cyclization precursors **5a**−**g**, which could be efficiently assembled from indium-mediated methallylation of 1-bromo-2-methyl-2-propene with corresponding bromoaldehydes **2a**−**g** in 80−90% yield[1] (Scheme 3).

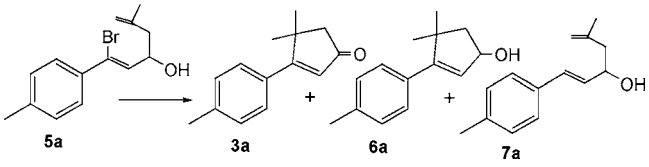
Scheme 3



When the precursors were subjected to Heck reaction conditions in the presence of bases other than sodium formate, gem dimethyl cyclopentenone derivatives were obtained. The reaction was then attempted by changing the base, solvent, and catalyst to optimize the reaction conditions (Table 1).

Because a terminating species is required for the generation of the gem dimethyl group, the reaction mixture containing

Table 1. Optimization Studies[a]



entry	catalyst	base	solvent	time (h)	**3a** (%)	**6a** (%)	**7a** (%)
1	$Pd(OAc)_2$/A	K_2CO_3	CH_3CN	8	28	20	40
2	$Pd(OAc)_2$/A	K_2CO_3	DMF	8	35	15	30
3	$Pd(OAc)_2$	HCOONa	DMF	3	0	55	10
4	$Pd(OAc)_2$	K_2CO_3	DMF	6	50	9	8
5	$Pd(OAc)_2$	Cs_2CO_3	DMF	9	40	12	3
6	$Pd(OAc)_2$	K_2CO_3	dioxane	8	45	3	20
7	$Pd(OAc)_2$	Na_2CO_3	toluene	12	12	0	35
8[b,c]	$Pd(PPh_3)_4$	Na_2CO_3	DMF	8	50	10	0
9	$Pd(OAc)_2$	Na_2CO_3	DMF	5	70	6	0

[a] All the reaction mixtures were heated to 80 °C. A: 1 equiv of sodium formate was added after the reaction mixture was heated for 2 h. [b] 0.5 equiv of PPh_3 was added to the reaction mixture in all the cases except entry 8. [c] 1 equiv of Bu_4NCl was added.

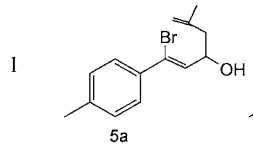
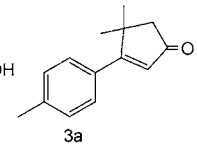
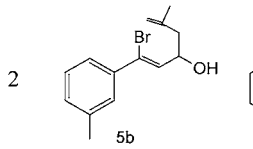
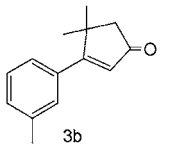
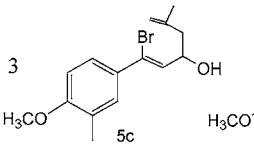
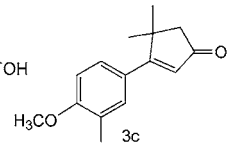
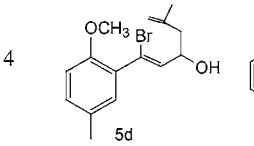
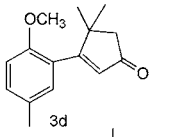
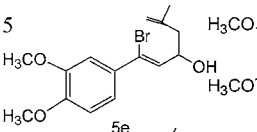
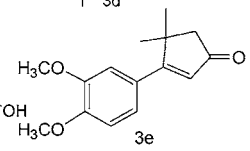
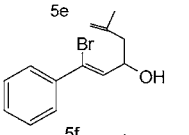
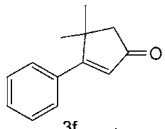
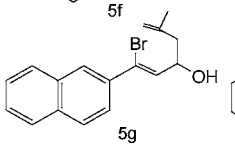
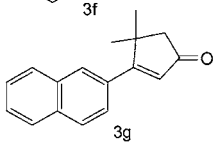
substrate **5a**, $Pd(OAc)_2$, base, and DMF was first heated for 2 h and then sodium formate was added to it as a terminator. However, we obtained the gem dimethyl substituted cyclopentenone derivative along with a significant amount of uncyclized, dehalogenated products. We then tried other options by eliminating the base and carrying out the reaction with sodium formate only. This time we obtained no keto compound, but the gem dimethyl substituted alcohol derivative along with a small amount of uncyclized dehalogenated substrates were the isolable products. This initial screening indicated that the keto derivative could not be obtained significantly in the presence of sodium formate. During our effort to find the appropriate conditions, we finally succeeded in getting our desired keto compound by eliminating sodium formate and carrying out the reaction in the presence of sodium carbonate. The terminating species must have come from the substrate itself, otherwise the gem dimethyl group could not have been generated.

Next, we investigated several additional solvents and bases to improve the yield of our desired product. The reaction also worked under ligandless conditions, but the yield was somewhat low. Finally, we concluded that, when the reaction was carried out with 2 mol % of $Pd(OAc)_2$, 0.5 equiv of PPh_3, and 1.5 equiv of Na_2CO_3 in DMF at 80 °C for 5 h, the yield of **3a** increased to 70% (Table 2).

Compound **3a** led to (±)-β-cuparenone (**8a**) in a single step (Scheme 4).[8]

In previous communications,[1] we were able to obtain the methyl-substituted oxidized product through the isomerization of an exocyclic double bond formed by intramolecular cyclization of the allylated and propargylated derivatives of vinyl bromoaldehyde. The possibility of formation of an exocyclic double bond could be discarded because of the unavailability of β-hydrogen for elimination after cyclization through a 5-exo-trig pathway. Still, we had isolated the gem

Table 2. Synthesis of Gem Dimethyl Cyclopentenone Derivatives through Palladium-Catalyzed Tandem Heck Cyclization of **5a**−**g**[a]

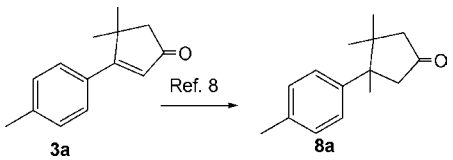
entry	substrates	products	yield (%)[b]
1			70
2			75
3			65
4			60
5			78
6			75
7			80

[a] All the reactions were carried out with 2 mol % of $Pd(OAc)_2$, 0.5 equiv of PPh_3, and 1.5 equiv of Na_2CO_3 in DMF at 80 °C for 5 h. [b] Isolated yields after purification.

dimethyl cyclopentenone derivative surprisingly as the major product. The mechanism hence seems to follow a different pathway (Scheme 5).

In a recent communication,[10] it has been established that in the absence of a terminating agent this type of substrate undergoes a 6-endo mode olefin insertion. In our case, 5-exo-trig cyclization occurred probably because of the presence of the −CHOH group which donated a hydride for termination, itself being converted to −C═O. By changing the reaction condition, i.e., using sodium formate as a hydride donor in the absence of base, we were able to isolate the cyclized unoxidized derivative as our isolable product. This might be because in the absence of base no hydride transfer occurred and hence no proton abstraction resulted to form the palladium hydride intermediate. The palladium bromide intermediate directly cyclized which in turn terminated through hydride capture from sodium formate to generate an unoxidized gem dimethyl cyclopentenol derivative (Table 3).

Scheme 4



Scheme 5. Mechanistic Pathway

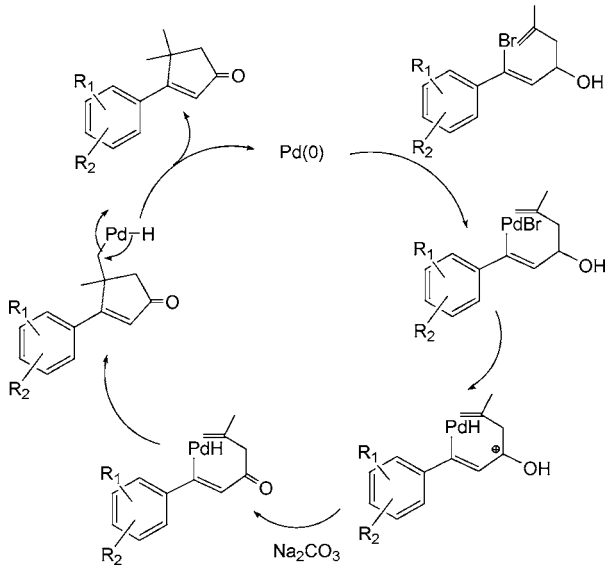


Table 3. Synthesis of Gem Dimethyl Cyclopentenol Derivatives[a]

entry	substrates	products	yield (%)[b]
1	**5a**	**6a**	50
2	**5b**	**6b**	56
3	**5f**	**6f**	60
4	**5g**	**6g**	58

[a] All the reactions were carried out with 2 mol % of $Pd(OAc)_2$, 0.5 equiv of PPh_3, and 1.2 equiv of HCOONa in DMF at 80 °C for 3 h. [b] Isolated yields.

So, we are able to establish two different reaction conditions to obtain two mechanistically different products, one of which directly leads to sesquiterpene precursors.

In conclusion, palladium-catalyzed intramolecular Heck cyclization has proven to be a practical, shorter, and good yielding means for the preparation of sesquiterpene precursors. We are gratified to prove that this methodology has the potential to be of great benefit in the convergent synthesis of a number of natural product moieties.

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Supporting Information Available: Complete experimental details along with spectroscopic data for new compounds synthesized. This material is available free of charge via the Internet at http://pubs.acs.org.

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