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Facile Construction of an α-(1-Cyclopentenyl)ketone Core by Ruthenium-Catalyzed Hydrative Cyclization of 1,6-Allenyne: Total Synthesis of (+)-Myomontanone

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Facile Construction of an α-(1-Cyclopentenyl)ketone Core by Ruthenium-Catalyzed Hydrative Cyclization of 1,6-Allenyne: Total Synthesis of (+)-Myomontanone

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Ruthenium-catalyzed hydrative cyclization of 1,6-allenyne in the presence of H_2O was demonstrated. The reaction proceeded via nucleophilic attack of H_2O to a ruthenacyclopentene intermediate, giving an α-(1-cyclopentenyl)ketone derivative under mild conditions. In addition, the total synthesis of (+)-myomontanone was achieved by using ruthenium-catalyzed hydrative cyclization of 1,6-allenye as a key step.

Keywords: 1,6-Allenyne, α-(1-cyclopentenyl)ketone, ruthenium

An α-(1-cyclopentenyl)ketone core is a key structure found in a number of biologically active natural products such as alterbrasone (Figure 1, **1**),[1] eucalmaidial A (**2**)[2] and 16-dehydropregnenolone (16-DHP, **3**).[3] Moreover, α-(1-cyclopentenyl)ketone derivatives have been recognized as useful building blocks for the synthesis of complex organic molecules.[4] Therefore, various methodologies for construction of the α-(1-cyclopentenyl)ketone core such as an intramolecular aldol condensation,[5a] [3+2] cycloaddition,[5b] intramolecular Rauhut-Currier reaction[5c] and Morita-Baylis-Hillman reaction[5d] have been developed.

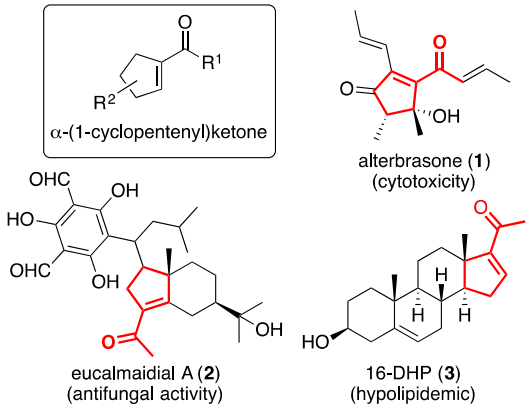
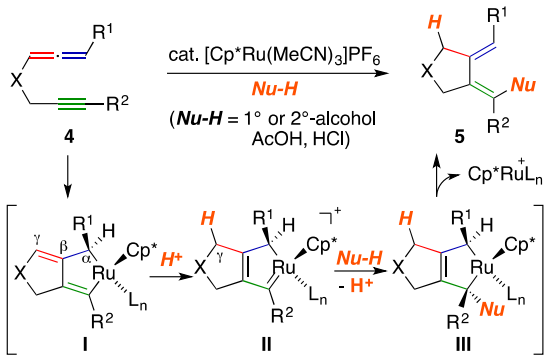


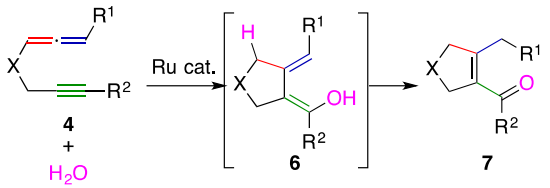
Figure 1. Representative bioactive molecules including an α-(1-cyclopentenyl)ketone core.

We previously reported regio- and stereoselective synthesis of 1,2-bisalkylidenecyclopentane derivatives **5** by ruthenium-catalyzed cyclization of 1,6-allenynes **4** via addition of nucleophiles to ruthenacyclopentenes (Scheme 1).[6] Thus, the reaction proceeded via formation of ruthenacycle **I** generated by oxidative cyclization of **4** to the ruthenium complex, from which protonation occurred at the γ-position of **I**, to give the ruthenium carbene intermediate **II**. Finally, addition of nucleophile (Nu-H) to the ruthenacycle **II** followed by reductive elimination from intermediate **III** resulted in production of the 1,2-bisalkylidenecyclopentane derivative **5**.



Scheme 1. Cyclization of 1,6-allenye via addition of nucleophile to ruthenacyclopentene.

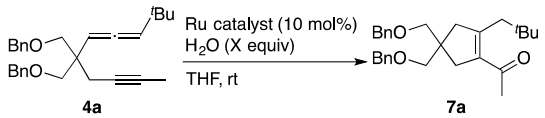
Based on the above background, we planned ruthenium-catalyzed cyclization of 1,6-allenyne in the presence of H_2O (Scheme 2). If the reaction of 1,6-allenyne **4** would proceed via addition of less nucleophilic H_2O, α-(1-cyclopentenyl)ketone derivative **7** could be obtained by tautomerization from dinenyl alcohol **6** under mild conditions.[7]



Scheme 2. Strategy for the construction of α-(1-cyclopentenyl)ketone by cyclization of 1,6-allenyne accompanied by addition of H_2O.

To examine the feasibility of the above plan, we first investigated reaction conditions (Table 1). 1,6-Allenyne **4a** was reacted with 10 equivalents of H_2O in the presence of 10 mol% of Cp*RuCl(cod) in THF at room temperature, giving **7a** in only 8% yield (run 1). When a $[Cp^*Ru(MeCN)_3]PF_6$ catalyst was used instead of Cp*RuCl(cod), **4a** was consumed within 2 hours, and **7a** was obtained in 74% yield (run 2). After investigation of the effects of quantity of H_2O on the yield of **7a** (runs 2-5), we found that hydrative cyclization of **4a** in the mixed solvent of THF and H_2O in a ratio of 10 to 1 proceeded smoothly to give **7a** in high yield (run 5).

Table 1. Optimization of reaction conditions.

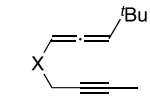
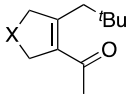
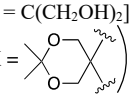
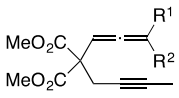
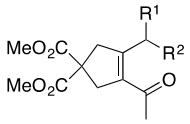
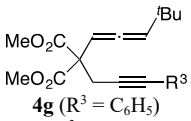
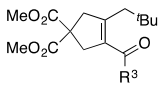


run	Ru catalyst	X (equiv)	time (h)	yield (%)
1	Cp*RuCl(cod)	10	19	8[a]
2	$[Cp^*Ru(MeCN)_3]PF_6$	10	2	74
3	$[Cp^*Ru(MeCN)_3]PF_6$	30	2	76
4	$[Cp^*Ru(MeCN)_3]PF_6$	60	5	78
5[b]	$[Cp^*Ru(MeCN)_3]PF_6$	-	2	80

[a] Allenyne **4a** was recovered in 74% yield.
[b] The reaction was carried out in a mixed solvent of THF and H_2O (v/v = 10/1).

With the optimal conditions in hand, we explored the substrate scope of the hydrative cyclization (Table 2). First, the structure of the linker part between allene and the alkyne moiety was investigated (runs 1-3). As a result, the reaction conditions were tolerated by not only 1,6-allenynes having an ester moiety **4b** and hydroxyl group **4c** but also those having acid-labile acetonide moiety **4d**, and the corresponding cyclized products **7b-d** were obtained in high yields. The reaction of a substrate bearing an isopropyl group on the allene part **4e** gave the cyclopentenylketone derivative **7e** in 68% yield (run 4). On the other hand, the reaction of allenyne having a terminal allene moiety **4f** gave no desired cyclized product **7f** (run 5).Finally, the effect of substituents on the alkyne part was examined (runs 6-10). As a result, it was found that various 1,6-allenyenes having aromatic groups or oxygen functionalities including an acid-labile siloxy or acetal moiety (**4g-k**) were applicable to the reaction conditions, and the corresponding cyclopentenylketone derivatives **7g-k** were obtained in good to high yields.

Table 2. Hydrative cyclization of vatious1,6-allenynes.[a]

run	substrate **4**	time (h)	yield (%)
			
1	**4b** [X = $C(CO_2Me)_2$]	2	**7b**: 84%
2	**4c** [X = $C(CH_2OH)_2$]	16	**7c**: 97%
3	**4d** 	16	**7d**: 94%
			
4	**4e** (R^1 = ^{i}Pr, R_2 = H)	16	**7e**: 68%
5	**4f** (R^1 = R^2 = H)	16	**7f**: -
			
6	**4g** (R^3 = C_6H_5)	16	**7g**: 89%
7	**4h** (R^3 = CH_2OH)	19	**7h**: 96%
8	**4i** (R^3 = CH_2OTBS)	19	**7i**: 63%
9	**4j** (R^3 = CH_2OAc)	16	**7j**: 64%
10[b]	**4k** (R^3 = CH_2OMOM)	5	**7k**: 82%

[a] Reaction conditions: $[Cp^*Ru(MeCN_3)_3]PF_6$ (10 mol%), [**4**] = 0.08M in THF/H_2O (10/1), room temperature
[b] The reaction was carried out at 50 °C.

Next, we turned our attention to the application of hydrative cyclization to total synthesis of furanosesquiterpene, (+)-myomontanone (Figure 2, **8**).[8] Myomontanone (**8**) is a major component that accounts for 70% of the essential oil contained in *Myoporumu montanum*, which belongs to the Myoporaceae family originating in Western Australia. In 1983, Sutherland's group isolated and determined the structure of **8**.[8a] Although Dinsdale and co-workers reported that a metabolic active substance of **8** caused lung injury and liver damage,[8b] the biological activity of **8** itself has not been determined. On the other hand, the only example of total synthesis **8** was demonstrated by Roussis' group.[9] In this context, we envisaged that if the above hydrative cyclization was applicable to the allenyne **9** having a 3-furyl group on the alkyne part, total synthesis of **8** could be achieved.

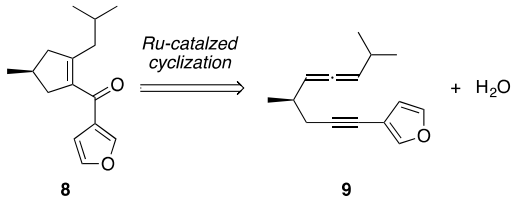
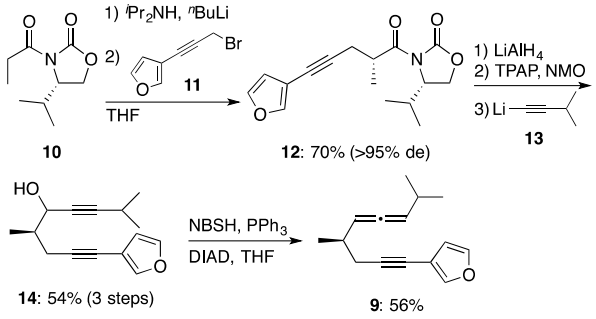


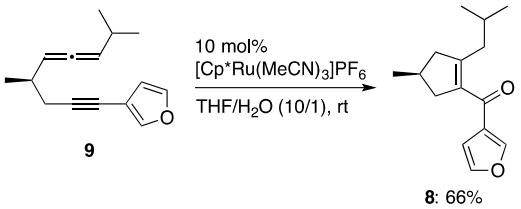
Figure 2. Structure of (+)-myomontanone (**8**).

Synthesis of allenyne **9** is shown in Scheme 3. Asymmetric Evans alkylation[10,11] of **10** with literature-known propargyl bromide **11**[12] provided **12** in 70% yield in a highly diastereoselective manner. Reductive removal of the oxazolidinone part from **12** followed by oxidation and alkylation with **13** generated from 3-methylbut-1-yne and ^{n}BuLi gave diyne derivative **14**. Finally, allenyne **9** was obtained by deoxygenation[13] of **14** by treatment of *o*-nitrobenzenesulfonylhydrazide (NBSH) under Mitsunobu conditions.



Scheme 3. Synthesis of allenyne **9** via asymmetric Evans alkylation

Ruthenium-catalyzed hydrative cyclization of **9** proceeded smoothly to give (+)-myomontanone (**8**), for which spectral data including the value of optical rotation were identical to those reported previously, in good yield (Scheme 4).[8]



Scheme 4. Synthesis of (+)-myomontanone (**8**)

In summary, we succeeded in the development of a synthetic methodology of α-(1-cyclopentenyl)ketone derivatives by ruthenium-catalyzed hydrative cyclization of 1,6-allenyne. Furthermore, concise total synthesis of (+)-myomontanone by the above hydrative cyclization was demonstrated. Further studies along this line are in progress.

Supporting Information

Electronic Supplementary Information (ESI) available: experimental procedures and characterization data, including ^{1}H and ^{13}C NMR spectra for new compounds. Supporting Information is available on http://dx.doi.org/10.1246/cl.******.

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