SYNTHESIS OF MEDIUM-SIZE LACTONES FROM ALKYNE USING CHROMIUM CARBENE COMPLEX

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Abstract — Reaction of alkynes having the hydroxy group in a tether with choromium carbene complex gave medium-size lactones in good to moderate yields. The two geminal substituents in a chain affect the yield of the lactones.

Recently, we reported the synthesis of the four-, five-, six-, and seven-membered lactones from alkynes having the hydroxy or silyloxy group in a tether with Fischer chromium carbene complex[1] in good yields *via* vinylchromium ketene complexes.[2]

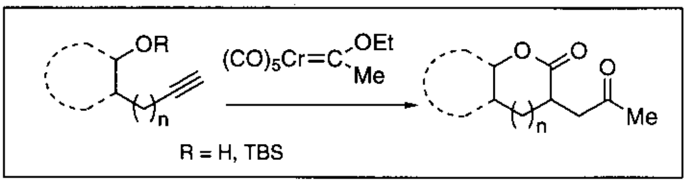

Figure 1

The reaction course is shown in Scheme 1. The important intermediate of this reaction is vinylchromium carbene complex **II**, which is in a state of equilibrium with vinylchromium ketene complex **III**. The hydroxy or silyloxy group in a tether attacks the ketene moiety to produce lactones **IV**. It was expected that if the alkyne chain is elongated, medium-size lactones would be obtained. Here, we report the synthesis of medium-size lactones

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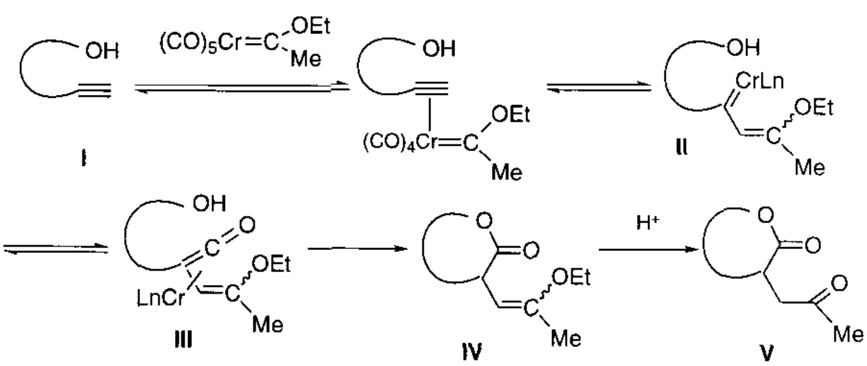
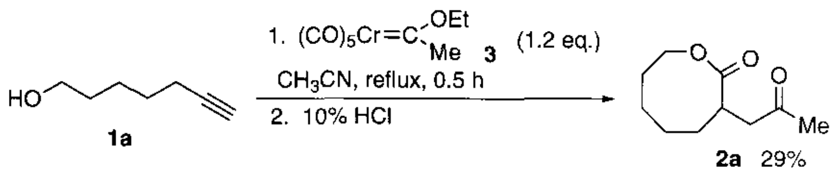
Dedicated to Professor Koji Nakanishi on the occasion of his 75th Birthday.

Reaction Mechanism



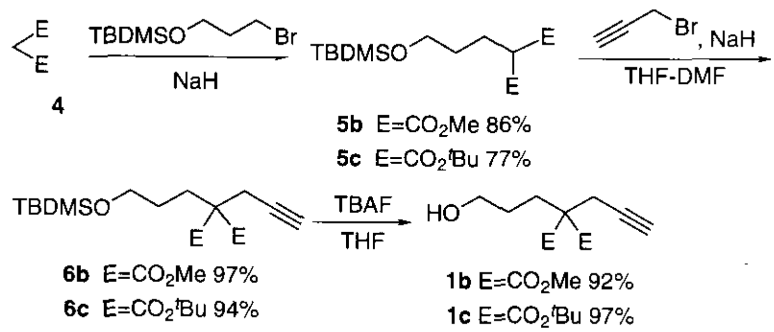
Scheme 1

from alkynes having the hydroxy group in a tether using chromium carbene complex. When a CH_3CN solution of **1a** and chromium carbene complex (1.2 equiv.) was refluxed for 30 min and then the reaction mixture was hydrolyzed, lactone (**2a**) was obtained in 29% yield. Although the yield was low, the eight-membered lactone was produced from alkyne (**1a**).



Scheme 2

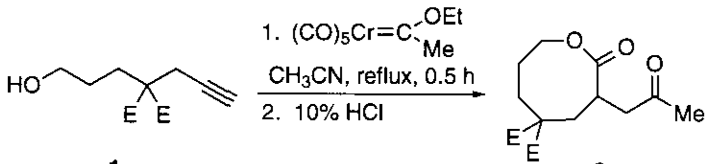
To improve the yield of the eight-membered lactone (**2**), the reaction of the alkyne having two substituents in the chain with chromium carbene complex was tried.



Scheme 3

Reaction of dimethyl malonate with alkyl halide in the presence of NaH produced **5b**, which was further treated with propargyl bromide in the presence of NaH to give **6b**.

Deprotection of the silyl group gave the starting alkyne (**1b**). In a similar manner, the alkyne (**1c**) having two tertiary butoxycarbonyl groups in the chain was prepared in good yield. Alkynes (**1b**) and (**1c**) were treated with chromium carbene complex (**3**) in a similar manner to give eight-membered lactones (**2b**) and (**2c**). As expected, the yields of **1b** and **1c** were improved (Table 1). Surprisingly, eight-membered lactone (**2c**) was obtained in 81% yield from alkyne (**1c**). The reason why the yields were improved when the alkynes have substituents in the chain was considered to be due to the geminal dialkyl effects, one of which is the Thorpe Ingold effect[3] and the other of which is the reactive rotamer effects.[4] To explain the latter effect, vinyl ketene complexes **IIIa** and **IIIc** are depicted by Newman projections (**7a**), (**7a'**), (**7c**), and (**7c'**), which we can sight along C(5)-C(4).



1 **Scheme 4** **2**

Table 1. Substituent Effects

run	E	substrate	yield (%)
1	H	**1a**	29
2	CO_2Me	**1b**	60
3	$CO_2{}^tBu$	**1c**	81

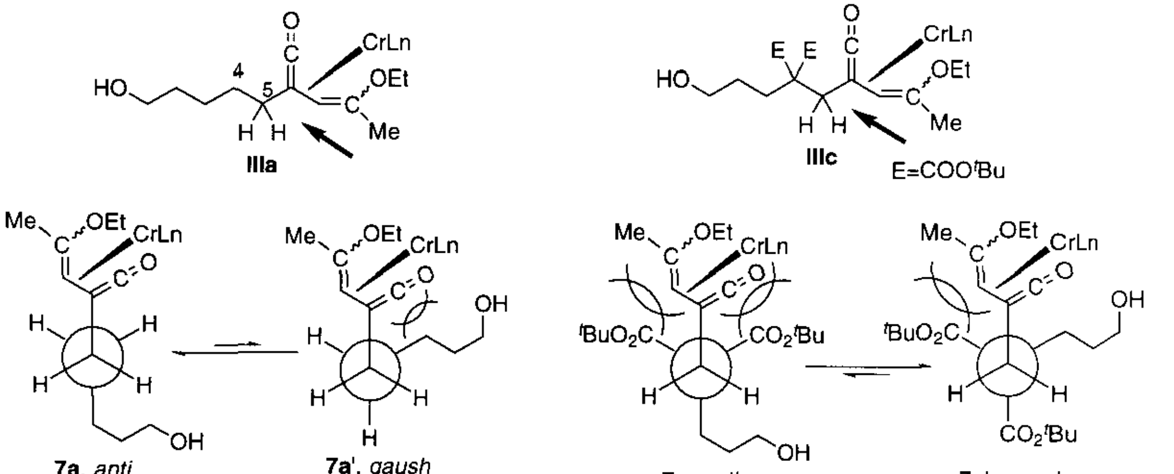
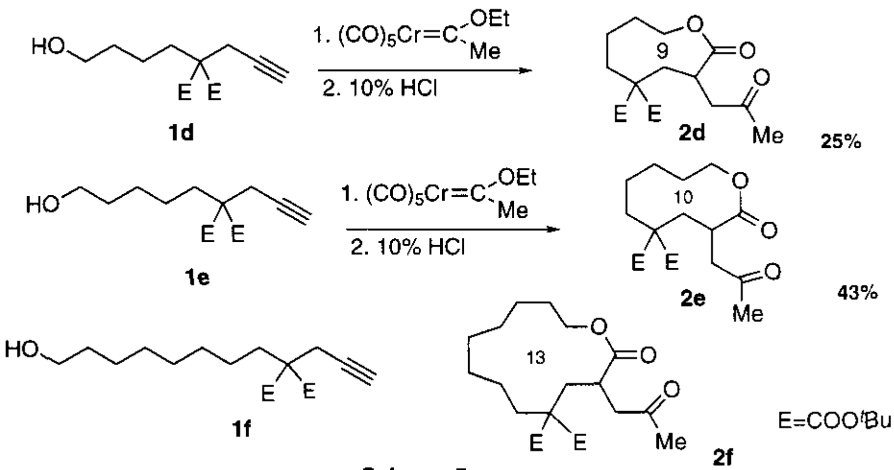


Figure 2

In the case of **IIIa** having no substituent in the chain, the anti-conformer (**7a**) is considered to have the lowest conformation energy and is more stable than **7a'** because of the steric hindrance between the large vinyl ketene moiety and the hydroxy part in **7a'**. Thus, the ethoxy group in the vicinity of the ketene attacks ketene to form five-membered compound.[2b] On the other hand, the anti-conformer (**7c**) is not stable in **IIIc** because of the steric hindrance between the two large tertiary butoxycarbonyl groups and the ketene moiety compared with those between the hydroxy part and the ketene moiety on **7c'**. Thus, the eight-membered lactone is easily formed from **7c'**.

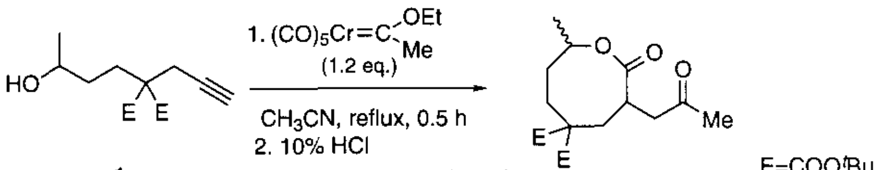
Subsequently, various medium-size lactones were prepared. Formation of nine- and ten-membered lactones were obtained in yields of 25% and 43%, respectively. However, the macrocyclic lactone (**2f**) was not produced from **1f**, because the difficulty in the formation of a large ring-size lactone could not be overcome by the geminal effect.



1d 1e 1f 2d 2e 2f

Scheme 5

In the formation of eight-membered lactone, alkyne (**1g**) having the secondary hydroxy group was examined and we obtained lactone (**2g**) in 64% yield.



1g 2g

Scheme 6

Further studies are now in progress.

REFERENCES AND NOTES

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