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New Lactone Synthesis Using a Chromium Carbene Complex

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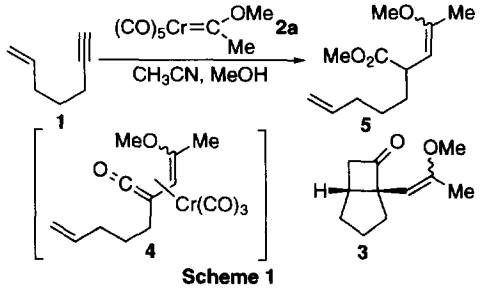
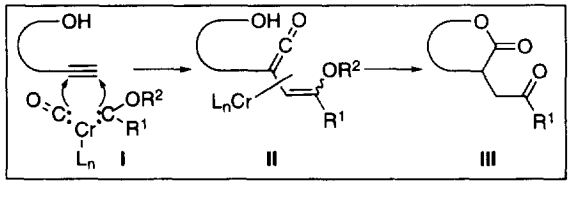
Abstract: A new lactone synthesis was developed using the Fischer chromium carbene complex. The lactone was formed from an alkyne bearing a hydroxyl or silyloxyl group in a tether, along with carbene carbon and carbon monoxide of the chromium carbene complex. Using this procedure, (+)-blastmycinone and (+)-antimycinone were synthesized from (*S*)-ethyl lactate in short steps.

Fischer chromium carbene complex is useful for synthetic organic chemistry, and various reactions have been reported.[1] Wulff reported that cyclobutanone **3** was formed by [2+2] cycloaddition of vinylketene and alkene of **4**, since the reaction of **1** with **2a** in the presence of MeOH gave ester **5** in moderate yield, and that the unactivated alkene did not react directly with the carbene complex.[2d] These results suggest that if an alkyne with a hydroxyl group in a tether **I** is treated with Fischer chromium carbene complex, lactone **III** would be formed *via* vinylketene complex **II** (Scheme 2).[2]

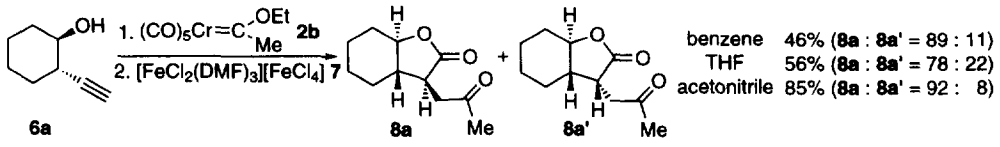


Scheme 1



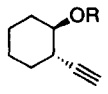
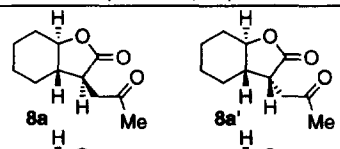
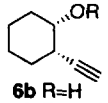
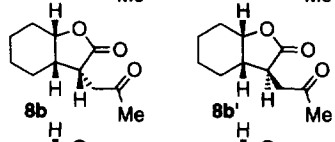
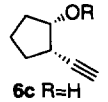
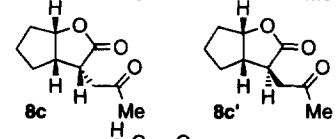
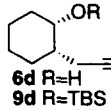
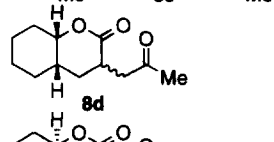
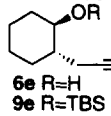
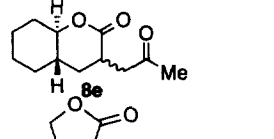
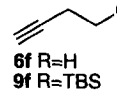
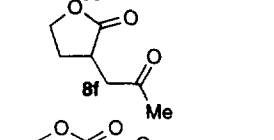
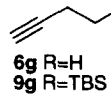
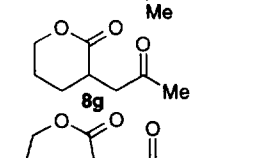
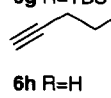
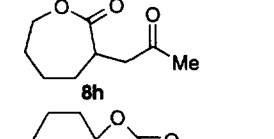
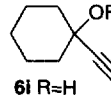
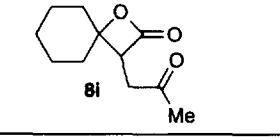
Scheme 2

A benzene solution of alkyne **6a** (1 equiv.) and chromium carbene complex **2b** (1.2 equiv.) was warmed at 70 °C for 30 min and then treated with $[FeCl_2(DMF)_3][FeCl_4]$[3] (**7**) (3 equiv.) to give lactones **8a** and **8a'** in 46% yield in a ratio of 9 to 1. In this reaction, the use of CH_3CN as a solvent gave a good result (85 % yield, **8a/8a'**=9/1). Various alkynes **6** with a hydroxyl group were treated with chromium carbene complex **2b** in a similar manner (Table 1). The reaction proceeded in a highly stereoselective manner, and the desired monocyclic and bicyclic lactones were obtained in good yields. The four-membered lactone **8i** was also obtained in moderate yield. Interestingly, the reactions of alkynes **9**, which have a silyloxyl group in a tether, with chromium carbene complex **2b** proceeded smoothly in a similar manner to give the corresponding lactones **8** and **8'** in good yields [Table 1, R=Si^{t}BuMe$_2$ (TBS)]. However, the stereoselectivity of **8** was not controlled.



Scheme 3

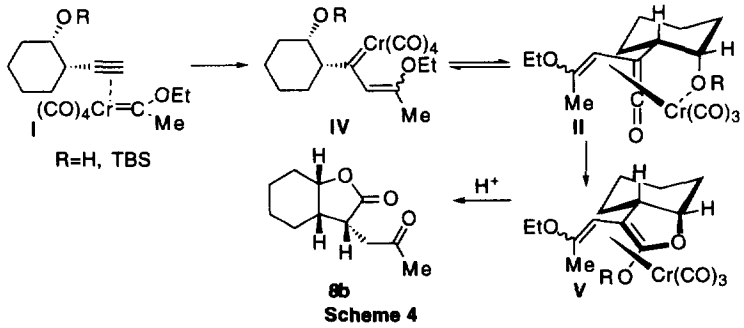
Table 1. Construction of Lactones from Various Alcohols and Silyl Ethers[a]

run	substrate	products (8:8')	yield (%)	ratio (8:8')
1	 **6a** R=H	 **8a** Me **8a'** Me	R=H	85 92 : 8
2	 **6b** R=H **9b** R=TBS	 **8b** Me **8b'** Me	R=H R=TBS	94 94 : 6 76 48 : 52
3	 **6c** R=H **9c** R=TBS	 **8c** Me **8c'** Me	R=H R=TBS	94 93 : 7 96 98 : 2
4	 **6d** R=H **9d** R=TBS	 **8d**	R=H R=TBS	78 70 : 30[b] 100 85 : 15[b]
5	 **6e** R=H **9e** R=TBS	 **8e**	R=H R=TBS	89 59 : 41[b] 57 66 : 34[b]
6	 **6f** R=H **9f** R=TBS	 **8f** Me	R=H R=TBS	86 43
7	 **6g** R=H **9g** R=TBS	 **8g** Me	R=H R=TBS	62 53
8	 **6h** R=H	 **8h** Me	R=H	63
9	 **6i** R=H	 **8i** Me	R=H	30

[a] Reactions were carried out in an CH_3CN solution at 70 °C.
[b] Relative configurations were not determined.

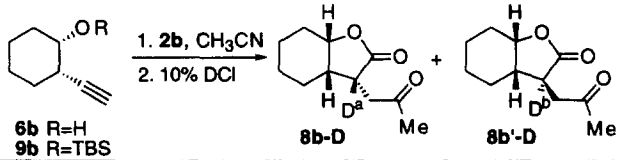
The reaction course for the formation of lactone **8** is considered to be as follows. The reaction of alkyne **6** with chromium carbene complex **2b** gives vinylcarbene complex **IV**, which is in a state of equilibrium with vinylketene complex **II**. The hydroxyl group then reacts intramolecularly with the ketene moiety of **II** to form complex **V**, which is hydrolyzed to give lactone **8**. The reaction of **6** with chromium carbene complex **2b**

proceeds in a highly stereoselective manner due to coordination of the hydroxyl group to chromium, which results in the hydroxyl group attacking the ketene moiety from the same side as chromium. Thus, protonation occurs from the same side as chromium to the α-position of the ester carbonyl group (Scheme 4). However, when the silyloxyl group attacks the ketene moiety of **II**, the ketene silylacetal **V** (R=TBS) would be formed. Thus, protonation occurs from both sides. To confirm this notion, when alkyne **9b** was reacted with **2b** in CH_3CN, and the reaction mixture was then treated with 10% DCl, the deuterated products **8b-D** (D-content, 62%) and **8b'-D** (D-content, 78%) were obtained in 61% yield (**8b-D**/**8b'-D**=1/1). On the other hand, when a reaction mixture of **6b** and **2b** was treated with DCl, none of the deuterated products were obtained.[4] These results indicate that the ketene silylacetal (**V**, R=TBS) was formed in the reaction of **9** with **2b**. Thus, we have successfully developed a new synthesis of α-substituted lactones from alkynes bearing a hydroxyl or silyloxyl group.



Scheme 4

Table 2. Incorporation of Deuterium at the Carbon α to Ester Carbonyl

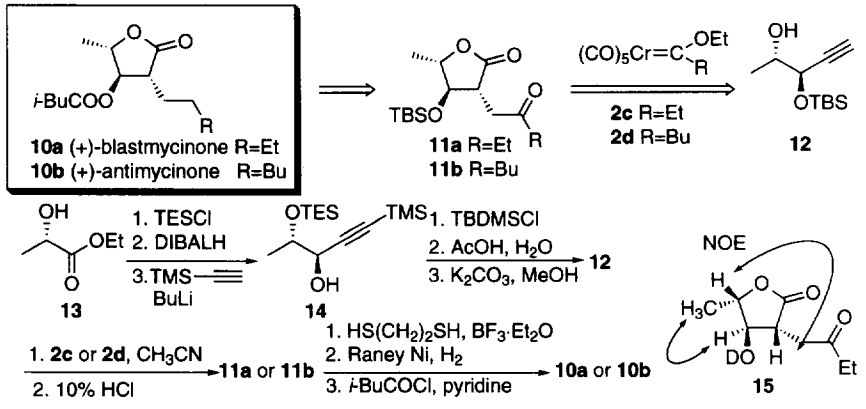


run	R	yield (%)	ratio (8b-D:8b'-D)	D content (%) D^a	D content (%) D^b
1	H (**6b**)	85	94: 6	0	0
2	TBS (**9b**)	61	54:46	62	78

We next tried to synthesize the natural products (+)-blastmycinone (**10a**) and (+)-antimycinone (**10b**).[5] These compounds should be easily obtained from lactone **11**. To prepare **11** using our procedure, alkyne **12** is required, which can be obtained from (*S*)-ethyl lactate (**13**). If the reaction of aldehyde, which is obtainable from (*S*)-ethyl lactate, with lithium acetylide proceeds according to the Felkin-Anh model, the desired alkyne **14** would be obtained.

Protection of (*S*)-ethyl lactate (**13**) with Et_3SiCl (TESCl) followed by treatment with DIBALH gave aldehyde, which was allowed to react with lithium TMS-acetylide to give alcohol **14** as an inseparable mixture. Then alcohol **14** was converted into the desired alkyne **12** in the usual manner (the ratio of *syn*- to *anti*-**12** is 1 to 4). The stereochemistry of compounds *syn*-**12** and *anti*-**12** were determined by NOE experiments of desilylated lactone **15**. As expected, the desired product *anti*-**12** was the main product. Reaction of alcohol **12** with chromium carbene complex **2c**, which was prepared by reacting $Cr(CO)_6$ and EtLi and then treating the

result with Et_3OBF_4, followed by acid hydrolysis gave lactone **11a** in 76% yield (The ratio at the carbon α to ester carbonyl is α/β=3/1). Thioketalization of **11a** in the presence of $BF_3 \cdot Et_2O$ was followed by treatment with Raney Ni under hydrogen and then with ^{t}BuCOCl in the presence of pyridine to give (+)-blastmycinone (**10a**). On the other hand, the reaction of **12** with chromium carbene complex **2d**, which was prepared from $Cr(CO)_6$ and BuLi as above, gave lactone **11b** in 71% yield (α/β=3/1). Treatment of **11b** as described above for **11a** gave (+)-antimycinone (**10b**). The spectral data and $[\alpha]_D$ values of **10a** and **10b** agreed with those of (+)-blastmycinone (**10a**)[5] and (+)-antimycinone (**10b**)[5], respectively.



Scheme 5 **Figure 1**

The significant characteristics of this reaction are as follows. α-Substituted lactones can be formed from alkynes bearing a hydroxyl or silyloxyl group and chromium carbene complex in a one-pot reaction. The reaction proceeds in a highly stereoselective manner. The α-substituent of the lactone can be easily changed by changing the alkyl lithium used to prepare the chromium carbene complex. Further studies are in progress.

References and Notes

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3. Tobinaga, S.; Kotani, E. *J. Am. Chem. Soc.*, **1972**, *94*, 309.
4. When a 10% DCl-CH_3CN solution of lactone **8b** was stirred at room temperature for 30 min, deuterated products were not obtained.
5. Recent reports on the synthesis of (+)-blastmycinone and (+)-antimycinone: (a) de Azevedo, M. B. M.; Greene, A. E. *J. Org. Chem.* **1995**, *60*, 4940. (b) Takahata, H.; Uchida, Y.; Momose, T. *J. Org. Chem.* **1994**, *59*, 7201. (c) Nishide, K.; Aramata, A.; Kamanaka, T.; Inoue, T.; Node, M. *Tetrahedron* **1994**, *50*, 8337.

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