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An Optically Active Chromium(0)-Complexed Benzaldehyde Derivative in Organic Synthesis: A Highly Stereocontrolled Total Synthesis of (+)-Goniofufurone

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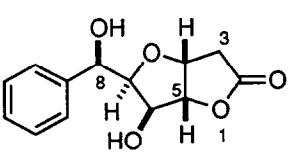
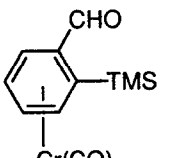
Abstract: An antitumor styryl-lactone, (+)-goniofufurone was synthesized in a highly diastereoselective manner from (+)-tricarbonyl(η^6-2-trimethylsilylbenzaldehyde)chromium(0) complex through stereoselective aldol reactions as crucial steps.

In 1990 (+)-goniofufurone (**1**), a representative novel styryl-lactone, was isolated from the stem bark of *Goniothalamus giganteus*[1] and shown to have significant cytotoxic activities toward human tumor cells.[1] Because of its cytotoxicity as well as intriguing structure, four groups have already completed total syntheses of natural[2] and unnatural[3] goniofufurone, (+)- and (-)-**1**, respectively. All methods[2,3] so far recorded for the synthesis of goniofufurone (**1**) utilized D-glucose as a chiral starting material.[4] We describe herein a highly stereoselective and efficient total synthesis of (+)-goniofufurone (**1**) from optically active chromium(0)-complexed benzaldehyde derivative **2**. Our strategy for the synthesis of (+)-**1** is based on diastereoselective aldol reactions which are obviously distinct from reported protocols.[2,3]

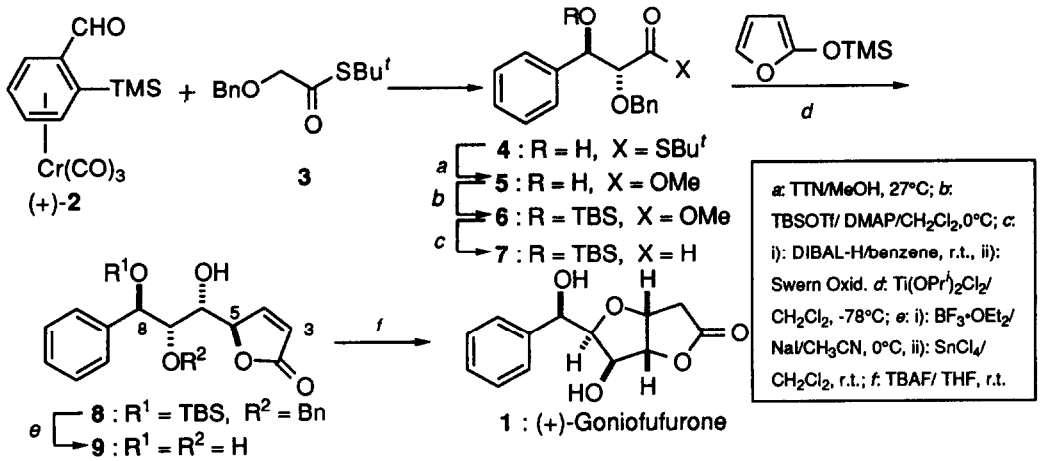


1 : (+)-Goniofufurone



(+)-**2**

According to our previous report,[5] the aldol product **4**[6] was easily prepared from *anti*-selective aldol reaction of (+)-**2** with the titanium enolate of thioester **3**. Treatment of **4** with thallium trinitrate in methanol[7] effected transesterification to provide the methyl ester **5**[6] in 71% yield, the hydroxy group of which was subsequently protected with *tert*-butyldimethylsilyl group (**6**[6]; 71%). Reduction of **6** with diisobutylaluminum hydride and subsequent Swern oxidation afforded the labile aldehyde **7**.[6] Because of its instability, **7** was immediately exposed to the aldol conditions where 2-trimethylsilyloxyfuran was employed as a carbon nucleophile under chelation-controlled situation[8] with dichlorotitanium diisopropoxide producing the γ-lactone **8**[9] in pure form in 54% overall yield from **6**. It is noteworthy that the aldol reaction between **7** and 2-trimethylsilyloxyfuran furnished all carbon framework required for goniofufurone skeleton with proper stereochemistry except for stereogenic center at C-5 that differs from that of goniofufurone. Successive desilylation (94%)[10] and debenzylation (96%)[11] of the γ-lactone **8**



yielded the triol **9**. Isomerization at C-5 stereogenic center of **9**, followed by spontaneous ring closure was realized by treatment with tetra-*n*-butylammonium fluoride in THF to give (+)-goniofufurone (**1**), mp 150-152°C (lit.[1] mp 152-154°C), $[\alpha]_D^{23}$ +8.9°(*c* 0.5, EtOH)[lit.[1] $[\alpha]_D^{22}$ +9.0°(*c* 0.5, EtOH)] in 86% yield. Synthetic (+)-goniofufurone was identified with natural one by comparison of ^{1}H- and ^{13}C-NMR spectra.

Thus, we succeeded in an efficient total synthesis of (+)-goniofufurone (natural form) in a highly stereocontrolled fashion from chiral chromium(0)-complexed benzaldehyde derivative.

Acknowledgement: We are indebted to Prof. J. L. McLaughlin, Purdue University, for providing the copies of ^{1}H- and ^{13}C-NMR spectra of natural (+)-goniofufurone.

References and Notes

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9 We have also accomplished total synthesis of (±)-goniofufurone from (±)-**2**. Structure of (±)-**8** was unambiguously established by X-ray analysis. These results combined with chiral protocol will appear in detail somewhere else in due course.

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