# Indium-mediated highly diastereoselective allenylation in aqueous medium: total synthesis of (+)-goniofufurone

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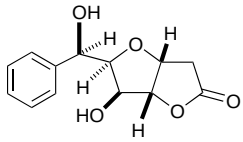
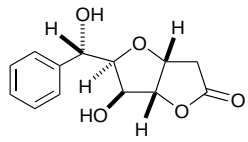
**(+)-Goniofufurone was synthesized from D-glucurono-6,3-lactone *via* an indium-mediated highly regio- and diastereo-selective allenylation of carbonyl compounds in aqueous medium.**

The Asian trees of the genus *Goniothalamus* have long been recognized as a potential source of chemotherapeutical agents. The extracts and leaves of *Goniothalamus* have traditionally been used for the treatment of edema and rheumatism,[1] a pain killer and a mosquito repellent,[2] as well as used as an abortifacient.[3] Recently, from the constituents of these plants, McLaughlin discovered a number of novel styryl lactones which were found to possess moderate to significant cytotoxicities against several human tumors. These findings have attracted considerable biological and synthetic attention to these styryl compounds. Among the key components in the extracts are (+)-goniofufurone **1**[4] and (+)-7-*epi*-goniofufurone **2**.[5] The



**1** (+)-Goniofufurone



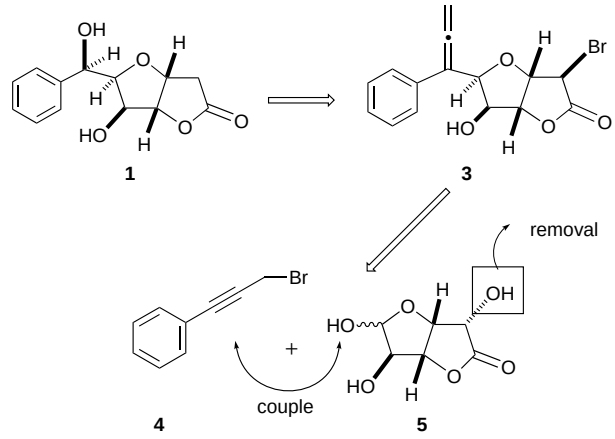
**2** (+)-7-*epi*-Goniofufurone

absolute stereochemistry of (+)-goniofufurone was established by Shing through the total synthesis of *ent*-(−)-**1**.[6] Subsequently, several synthetic studies have been carried out on the synthesis of **1**.[7–13]

The recent advances in Barbier–Grignard type carbon–carbon bond formations in aqueous medium[14] offer opportunities to synthesize various heavily oxygenated biologically important agents in a concise manner. Out continued interest in metal mediated carbon–carbon bond formation in aqueous media, particularly the synthetic application of these reactions, drew our attention to these styryl compounds. Here we report a highly regio- and diastereo-selective indium-mediated allenylation[15,16] of carbonyl compounds in aqeuous medium, which leads to a concise total synthesis of (+)-goniofufurone from a readily available starting material. The retrosynthetic analysis of (+)-goniofufurone is illustrated in Scheme 1.

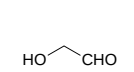
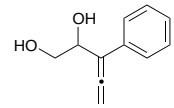
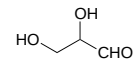
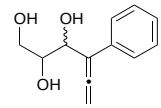
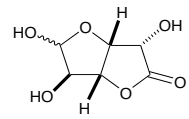
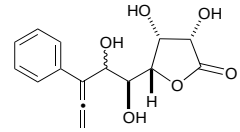
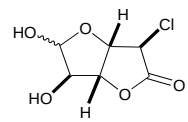
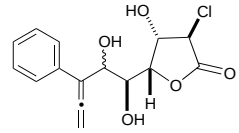
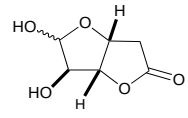
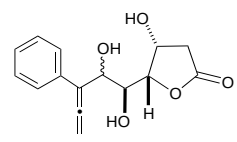
Initially, the coupling between 1-phenyl-3-bromopropyne and several carbohydrate substrates mediated by indium were investigated in aqueous EtOH (Table 1). In each case, the corresponding allenylation product was obtained with high diastereoselectivity, favoring the *syn* diastereomer. The high diastereoselectivity of this indium-mediated allenylation reaction could be attributed to chelation control.[17]

The results of the allenylation study confirmed the key step for the outlined synthesis. Thus, the commercially available D-glucurono-6,3-lactone **5** was readily converted into the corresponding bromo compound **6** based on the modification of a literature procedure for synthesizing a related chloro derivative.[18] Then allenylation of the compound with prop-2-ynyl bromide **4**, mediated by indium in aqueous EtOH, generated a mixture of allenylation products (56%) in which the allene **7** is the major component, together with debromination and re-

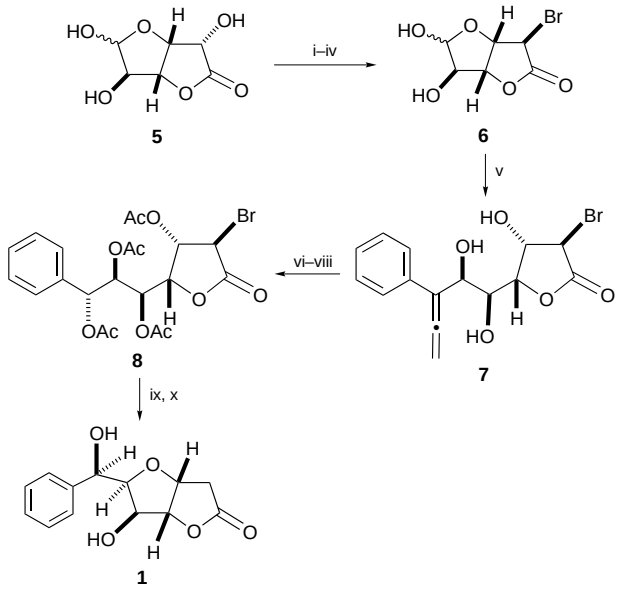



**Scheme 1**

**Table 1** Diastereoselective allenylation of carbonyl compounds

| Entry | Carbonyl compound | Product | Diastereo-selectivity | Yield (%)[a] |
|---|---|---|---|---|
| 1 |  |  | — | 57 |
| 2 |  |  | (10:1) | 63[b] |
| 3 |  |  | (>10:1) | 63[b] |
| 4 |  |  | (9:1) | 72 |
| 5 |  |  | (8:1) | 49[b] |

[a] The yields were those of the isolated major isomers after column chromatograph on silica gel and were not optimized. [b] Determined after peracetylation. Conditions: stirred in 0.1 M aq. HCl–EtOH (1 : 9) overnight at room temperature.




**Scheme 2** *Reagents and conditions*: i, acetone, $H_2SO_4$, room temp., 5 h, 86%; ii, $Tf_2O$, Py, $CH_2Cl_2$, −40 °C, 94%; iii, LiBr, acetone, room temp., 1 h, 97%; iv, TFA–$H_2O$ (3 : 1), room temp., 4.5 h, 98%; v, **4**, In, 0.1 M HCl–EtOH (1 : 9), room temp., 14 h; vi, $O_3$, MeOH, −78 °C, then DMS; vii, $NaBH_4$, MeOH, −10 °C, 30 min, then AcOH quench; viii, $H_2SO_4$, $Ac_2O$, room temp., 75% from **7**; ix, $Na_2HSO_3$, $Na_2SO_3$, MeOH–$H_2O$, room temp., 3 h, quant.; x, HCl (g), MeOH, room temp., 2 d, 44% from **8**

ductive elimination products. The allene **7** again shows a high ( > 10 : 1) *syn* diastereoselectivity (the desired isomer). Standard ozonolysis of the allene compound in MeOH, followed by a diastereoselective reduction with $NaBH_4$, provided the corresponding alcohol as the predominant product (de = 3 : 1). The initial assignment of the stereochemistry for the reduction was confirmed after completion of the total synthesis. Subsequent reaction of the polyol with conc. $H_2SO_4$ in $Ac_2O$ generated the peracetylation product **8** (*ca.* 75% from **7**) which decomposed on silica gel. Direct treatment of the peracetylation product with $Na_2HSO_3$ and $Na_2SO_3$ in MeOH–$H_2O$ generated an α,β-unsaturated γ-lactone, as shown by $^1$H NMR analysis of the crude material. In order to remove the acetyl protecting groups, the crude product was treated with HCl in MeOH resulting in the deprotected product which cyclized *in situ* giving the target natural product in 44% yield over two steps. The spectroscopic data and melting point of the target molecule synthesized by this method are consistent with previous literature reports.[7]

In conclusion, (+)-goniofufurone has been synthesized in a short sequence from D-glucurono-6,3-lactone using an indium-mediated, highly regio- and diastereo-selective allene formation in aqueous medium. The scope and application of the current indium-mediated method to the syntheses of other carbohydrates is presently under investigation.

## Notes and References

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1 Y. C. Wu, C. Y. Duh, F. R. Chang, G. Y. Chang, S. K. Wang, J. J. Chang, D. R. McPhail, A. T. McPhail and K. H. Lee, *J. Nat. Prod.*, 1991, **54**, 1077.
2 S. K. Talapatra, D. Basu, T. Deb, S. Goswami and B. Talapatra, *Indian J. Chem., Sect. B*, 1985, **24**, 29.
3 T. W. Sam, C. S. Yeu, S. Matsjeh, E. K. Gan, D. Razak and A. L. Mohamed, *Tetrahedron Lett.*, 1987, **28**, 2541.
4 X. P. Fang, J. E. Anderson, C. J. Chang, P. E. Fanwick and J. L. McLaughlin, *J. Chem. Soc., Perkin Trans. 1*, 1990, 1655.
5 X. P. Fang, J. E. Anderson, C. J. Chang, J. L. McLaughlin and P. E. Fanwick, *J. Nat. Prod.*, 1991, **54**, 1034.
6 T. K. M. Shing and H. C. Tsui *J. Chem. Soc., Chem. Commun.*, 1992, 432.
7 T. K. M. Shing, H. C. Tsui and Z. H. Zhou, *J. Org. Chem.*, 1995, **60**, 3121 and references cited therein.
8 T. K. M. Shing, H. C. Tsui and Z. H. Zhou, *J. Chem. Soc., Chem. Commun.*, 1992, 810.
9 P. J. Murphy and S. T. Dennison, *Tetrahedron*, 1993, **49**, 6695.
10 K. R. C. Prakash and S. P. Rao, *Tetrahedron*, 1993, **49**, 1505.
11 M. Tsubuki, K. Kanai and T. Honda, *Synlett*, 1993, 653.
12 C. Mukai, I. J. Kim and M. Hanaoka, *Tetrahedron Lett.*, 1993, **34**, 6081.
13 J. Ye, R. K. Bhatt and J. R. Falck, *Tetrahedron Lett.*, 1993, **34**, 8007.
14 C. J. Li, *Tetrahedron*, 1996, **52**, 5643.
15 M. B. Isaac and T. H. Chan, *J. Chem. Soc., Chem. Commun.*, 1995, 1003.
16 E. Kim, D. M. Gordon, W. Schmid and G. M. Whiteside, *J. Org.. Chem.*, 1995, **58**, 5500.
17 L. A. Paquette and T. M. Mitzel, *J. Am. Chem. Soc.*, 1996, **118**, 1931.
18 H. Parolis, *Carbohydr. Res.*, 1983, **114**, 21.

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