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Asymmetric Total Synthesis of (+)-Goniopypyrone

Wei-Shan Zhou* and **Zhi-Cai Yang**

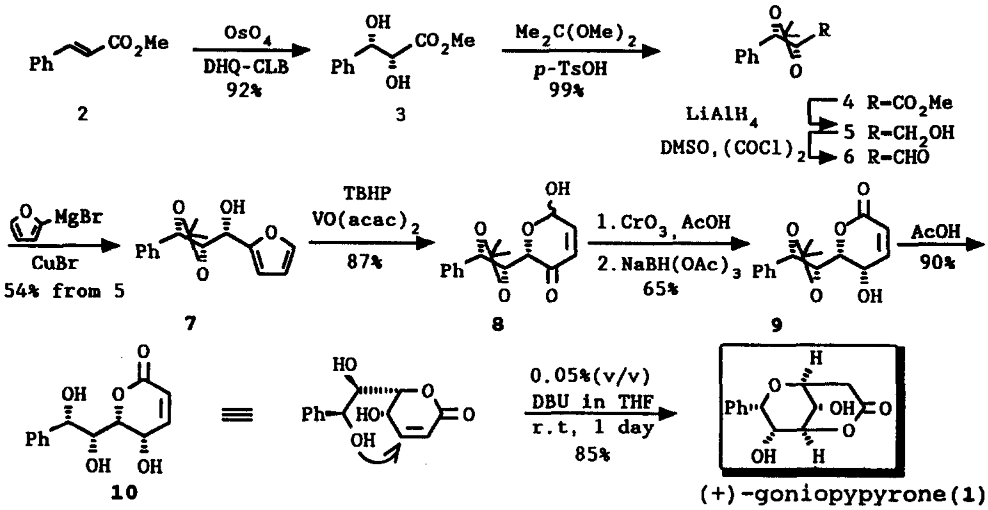
Shanghai Institute of Organic Chemistry, Chinese Academy of
Sciences, 354 Fenglin Lu, Shanghai 200032, China

Abstract: An effective asymmetric total synthesis of (+)-goniopypyrone from methyl cinnamate (**2**) via OsO_4 catalytic asymmetric dihydroxylation and highly stereoselective 2-furylcopper addition in eight steps with an overall yield of 20% is described.

A styryl lactone, (+)-goniopypyrone(**1**), was recently isolated from the stem bark of *Goniothalamus giganteus*[1] and shown to have significant cytotoxic activity[2]. Lately, Shing *et al* achieved the total synthesis of **1** from D-glycero-D-gulo-heptono-γ-lactone, also confirming its absolute configuration[3]. Herein, we report the total synthesis of **1** involving asymmetric dihydroxylation of methyl cinnamate(**2**) and highly stereoselective addition of 2-furylcopper to **6**.

The synthetic route to **1** is depicted in the scheme. Asymmetric dihydroxylation[4] of inexpensive **2** with dihydoquinine-4-chloro-benzoate (DHQ-CLB) as the added chiral ligand and potassium ferricyanide as the cooxidant produced the expected diol **3**, m.p. 80.5~81.5°C, $[\alpha]^{20}+10.7$(c 1.5, $CHCl_3$), >98%e.e[5]. Protection of **3** with 2,2-dimethoxy propane in the presence of *p*-TsOH furnished the desired **4**[6], $[\alpha]^{20}-43.4$(c, 1.5, EtOH). Reduction of ester **4** with $LiAlH_4$ gave alcohol **5**[6], $[\alpha]^{20}+32.7$(c 1.2, EtOH). Swern oxidation of **5** followed by immediate addition of 2-furylcopper[7], prepared from furyl Grignard reagent[8] and CuBr, to the liberated aldehyde **6** gave the *syn* adduct **7**[6] (the ratio of *syn* to *anti* adduct was determined to be 98.7:1.3 by GC), whereas reaction of **6** with 2-furyllithium only gave 2.5:1 *syn* selectivity (the data of ^1H NMR for the furyl proton of *tert*-butyldimethylsilylether of **7**: *syn*, δ 5.01, J=5.3 Hz; *anti*, δ 4.91, J=3.0 Hz[9]). Oxidation of **7** by TBHP/cat.$VO(acac)_2$ smoothly afforded the hydropyranone **8** as a mixture (3:1) of α- and β-anomers. Subsequent oxidation of the anomeric mixture of **8** with CrO_3-AcOH followed by stereoselective reduction of α,β-unsaturated lactone with $NaBH(OAc)_3$ in 1:1 mixture of isopropyl alcohol and acetic acid[10] at -10°C gave an unseparable mixture of hydropyanone **9**[6], the ratio of the two isomers (α-OH and β-OH) was determined to be 9:1 based on the ^1H NMR analysis. Acid hydrolysis of the acetone group in **9** furnished the known triol **10**[3], m.p.133~

134°C, $[\alpha]^{20}$+53(c 0.5, EtOH). Intramolecular Micheal reaction of **10** was mediated by a catalytic amount of DBU in THF to give **1** as colorless needles, m.p. 182~183°C, $[\alpha]^{20}$+54.1 (c 0.5, EtOH) [lit.[1] m.p. 182~184°C, $[\alpha]^{20}$+54(c 0.5, EtOH), lit.[3] m.p.180~182°C, $[\alpha]^{20}$+55.5(c 0.6, EtOH)].



The streamlined approach to (+)-goniopypyrone **1** presented here showed simply the preparation of the remaining styryl lactone. The preparation of 9-deoxygoniopypyrone, goniofufurone, goniodoil and goniotriol is in progress in our laboratory.

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