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A Short and Efficient Total Synthesis of The Cytotoxic (+)-Goniodiol and (+)-9-Deoxygoniopypyrone

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Abstract : (+)-Goniodiol **7** and (+)-9-deoxygoniopypyrone **8**, belonging to the group of styryllactones, have been synthesized in five steps and 75% yield respectively from C_4-esters **1a** and **1b**. The key step of these syntheses is a triflate-sulfone coupling which allowed a rapid construction of the backbone of the title compounds as well as the efficient installation of a masked *Z*-acrylate moiety.

Keywords : antitumor compounds, coupling reactions, lactones, sulfones.

The Asian trees of the genus *Goniothalamus* have been long recognized as a source of chemotherapeutic agents. The extracts and leaves of *Goniothalamus* have traditionally been used for the treatment of edema and rheumatism,[1a] as well as a pain killer and arbortifacient.[1b-c] Bioactivity-directed studies on the constituents of these plants by Mc Laughlin and Coll. have led to the isolation of several classes of biologically active compounds (acetogenins, alkaloids, styryllactones).[2] Among the styryllactones, (+)-goniodiol **7** and (+)-9-deoxygoniopypyrone **8** showed significant cytotoxicities against several solid tumor cell lines.[3] Because of their unique structural features and potent biological activities, several groups have paid attention to the synthesis of these two styryllactones.[4] In the course of our program directed toward the stereoselective synthesis of styryllactones, we have recently completed the total synthesis of six of them.[5] Herein, we report a short synthesis of styryllactones **7** and **8** from a common precursor, the ester **1a**.

The synthesis of goniodiol **7** began by $LiAlH_4$ reduction of the readily available ester **1a** from (*R*)-mandelic acid.[5c] Triflation of the resulting alcohol **2a**, according to the protocol described by Ambrose and Binkley,[6] furnished in nearly quantitative yield compound **3a**. The stage was now set up for the introduction of the *Z*-acrylate surrogate **4** by the Ghosez' methodology.[7] Displacement of the triflate **3a** by lithium salt of methyl 3-phenylsulfonylorthopropionate **4** occurred smoothly at -78°C, in the presence of HMPA, to furnish after mild acid treatment the sulfone **5a**[8] in 97% yield as an equal and unseparable mixture of diastereomers. Acid treatment of compound **5a** effected cleavage of the silyl and acetal protecting groups and lactone formation to give **6a** in 88% yield. Finally, subjection of **6a** to DBU induced elimination of $PhSO_2H$ to afford quantitatively goniodiol **7**.[9] Next, we turned our attention to the synthesis of 9-deoxygoniopypyrone **8**. Firstly, the ester **1b**, readily available in four steps and 75% yield from **1a**,[5e] was transformed by a two-step sequence, to the triflate **3b**. Surprisingly, unlike the coupling reaction between **3a** and **4**, that involving **3b** and **4** was best effected without HMPA at room temperature.[10] Treatment of the β-sulfonyl ester **5b** by trifluoroacetic acid, followed by exposure of the resulting lactone **6b** to DBU, which induced $PhSO_2H$ elimination and concomitant intramolecular Michael addition reaction, provided crystalline (+)-9-deoxygoniopypyrone **8**.[9]

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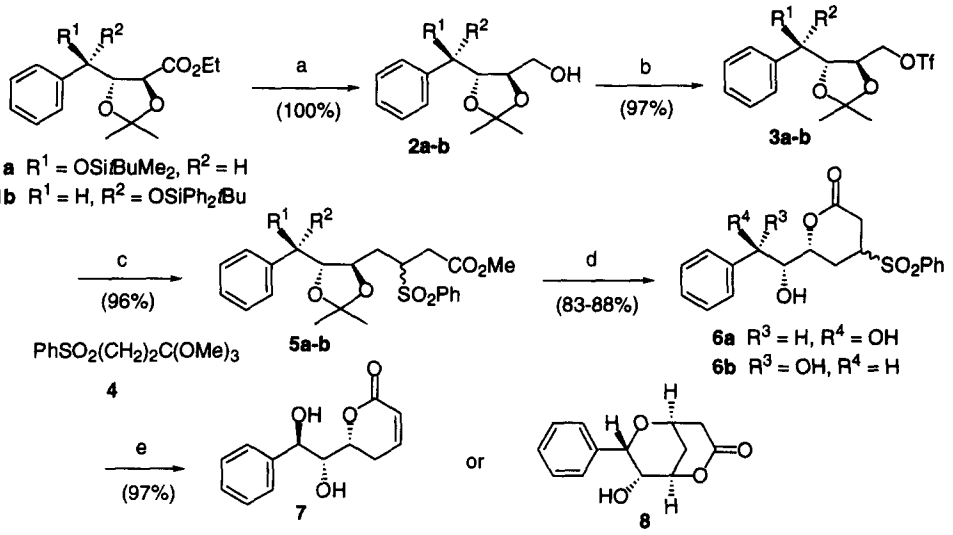

Reagents and conditions: (a) $LiAlH_4$, Et_2O, 0°C, 5min; (b) $(CF_3SO_2)_2O$, 2,6-di-t-butyl-4-methylpyridine, CH_2Cl_2, -10°C, 30 min; (c) **4** (3 equiv), *n*BuLi (3 equiv), solvent (see text); (d) CF_3CO_2H-H_2O, (4:1), RT, 18h; (e) DBU (3 equiv), CH_2Cl_2, 0°C, 1 h.

In summary, we have shown herein that the combination of the availability of the starting material **1a** with the valuable Ghosez's homoenolate reagent **4** and the efficient triflate-sulfone coupling allowed the preparation of multigram quantities of styryllactones **7** and **8** in a short sequence.

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8.Analytical and spectral data were obtained for all new compounds and are consistent with the structure assigned.
9. Synthetic (+)-goniodiol and (+)-9-deoxygoniopypyrone display physical and spectroscopic data in agreement with those of natural compounds (ref. 3).
10. Indeed, in the presence of HMPA, beside **5b** obtained in 50-77% yield was isolated compound **9** in 20-30% yield.