

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

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Received 10 June 1998; accepted 24 July 1998

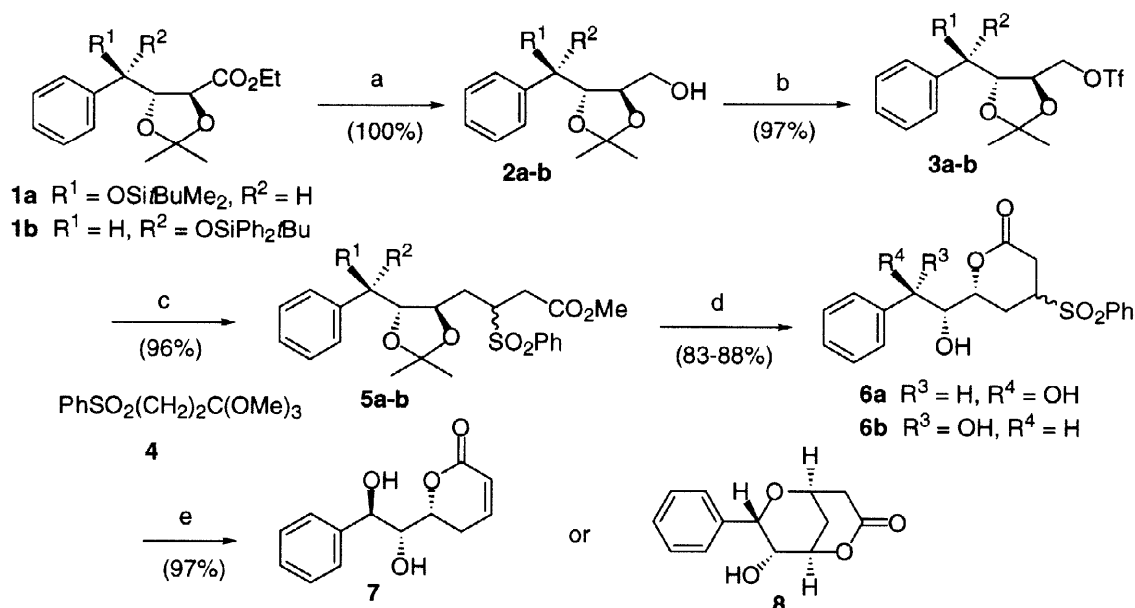
Abstract : (+)-Goniodiol **7** and (+)-9-deoxygonioppyrone **8**, belonging to the group of styryllactones, have been synthesized in five steps and 75% yield respectively from C₄-esters **1a** and **1b**. The key step of these syntheses is a triflate-sulfone coupling which allowed a rapid construction of the backbone of the title compounds as well as the efficient installation of a masked Z-acrylate moiety. © 1998 Elsevier Science Ltd. All rights reserved.

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 abortifacient.^{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-deoxygonioppyrone **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 LiAlH₄ 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 PhSO₂H to afford quantitatively goniodiol **7**.⁹ Next, we turned our attention to the synthesis of 9-deoxygonioppyrone **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 PhSO₂H elimination and concomitant intramolecular Michael addition reaction, provided crystalline (+)-9-deoxygonioppyrone **8**.⁹

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Reagents and conditions: (a) LiAlH_4 , Et_2O , 0°C , 5 min; (b) $(\text{CF}_3\text{SO}_2)_2\text{O}$, 2,6-di-*t*-butyl-4-methylpyridine, CH_2Cl_2 , -10°C , 30 min; (c) **4** (3 equiv), $n\text{BuLi}$ (3 equiv), solvent (see text); (d) $\text{CF}_3\text{CO}_2\text{H}-\text{H}_2\text{O}$, (4:1), RT, 18 h; (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.

Acknowledgments : We wish to thank Professor J. Goré for useful discussions and the Ministère de l'Enseignement Supérieur et de la Recherche for a fellowship to JPS.

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

