Proangiogenic Agents Unveiled:

Synthetic Pathways and Challenges in Prunolactone Chemistry

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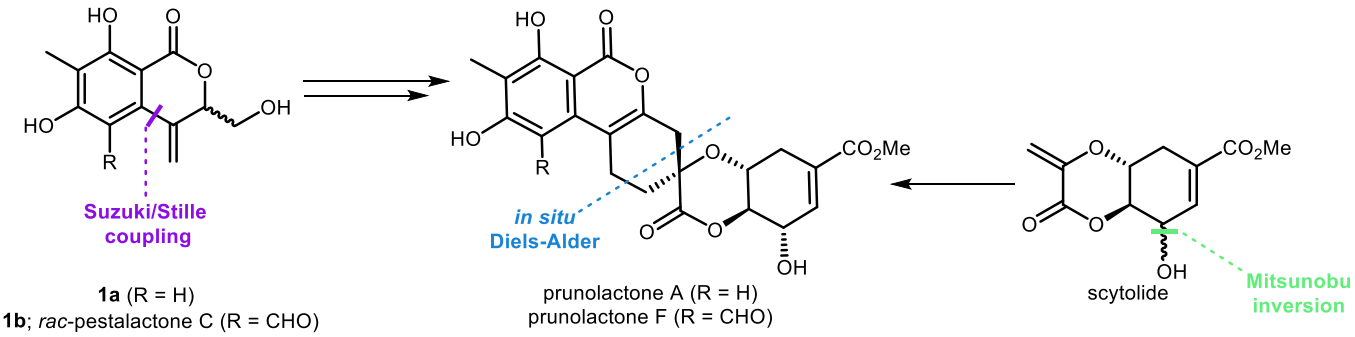
Over the past decade, *Phomopsis* fungi have produced over 250 bioactive compounds, several of which show interesting drug development potential. Among these, prunolactones A–G, isolated in 2023 from *Phomopsis prunorum*, stand out due to their rare 6/6/6/6/6 spiropentacyclic skeleton and notable proangiogenic activity[1]. Their biosynthesis is proposed to proceed *via* a Diels-Alder reaction between scytolide (Scheme 1), derived from the shikimate pathway, and a 3,4-bis(methylene)isocoumarin diene, generated by the dehydration of isocoumarin **1** (R = H or CHO)[1].

This work is focused on the preparation of prunolactone F. The naturally occurring isocoumarin, *rac*-pestalactone C (**1b**), is employed as a key starting material, synthesized *via* multiple routes, including green chemistry methodologies[2]. Finally, the total synthesis of the novel proangiogenic agent is accomplished in a concise 10-step sequence from (–)-shikimic acid, including a pivotal biomimetic Diels-Alder cycloaddition, which underscores the efficiency and elegance of the approach.



Scheme 1

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[1] Zhang, X.-Q.; Lu, Z.-H.; Tang, G.-M.; Duan, L.-P.; Wang, Z.-H.; Guo, Z.-Y.; Proksch, P. Bioorg. Chem. **2023**, 141.

[2] Wilson, K. L; Kennedy, A. R; Murray, J.; Greatrex, B.; Jamieson, C. Beilstein Journal of Organic Chemistry. **2016**, 12.