Total Synthesis of (+)-Penicyclone A and Bioactivity Assessment of Intermediate Compounds

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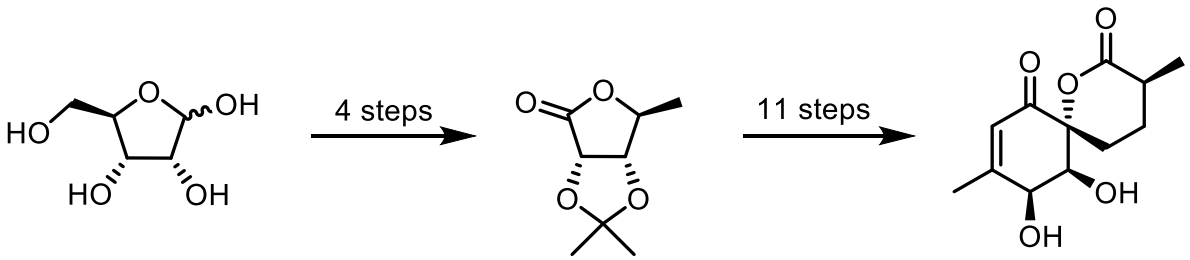
Penicyclones A – E are polyketide secondary metabolites isolated from the deep sea-derived fungus *Penicillium* sp. F23-2 during an OSMAC (One Strain Many Compounds) campaign [1]. All compounds exhibited notable antimicrobial activity, with penicyclone A having the lowest MIC (minimum inhibitory concentration) for *S. aureus*. The unique spiro[5.5]lactone structural motif in penicyclone A, along with its bioactivity, prompted us to pursue the total synthesis of the reported enantiomer [2]. However, the synthetic sample of penicyclone A failed to reproduce the antimicrobial activity observed in the natural product. Further analysis suggested that the natural product may, in fact, be the opposite enantiomer of that originally reported. Considering that many natural products occur as racemates [3], we synthesized the opposite enantiomer using our previously developed approach and evaluated the biological activity of both the final compound and selected intermediates.



D-ribose (+)-penicyclone A

[1] W. Guo, Z. Zhang, T. Zhu, Q. Gu, D. Li, *J. Nat. Prod.*, **2015**, *11*, 2699-2703.

[2] G. Talajić, E. Topić, J. Meštrović, N. Cindro, *J. Org. Chem.*, **2022**, *87*, 16054-16062.

[3] G. T. M. Bitchagno, V.-A. Nchiozem-Ngnitedem, D. Melchert, S. A. Fobofou, *Nat. Rev. Chem.*, **2022**, *6*, 806-822.