Studies toward an Improved Synthesis of Anti-tumour Natural Products Pseudolaric Acid A and B

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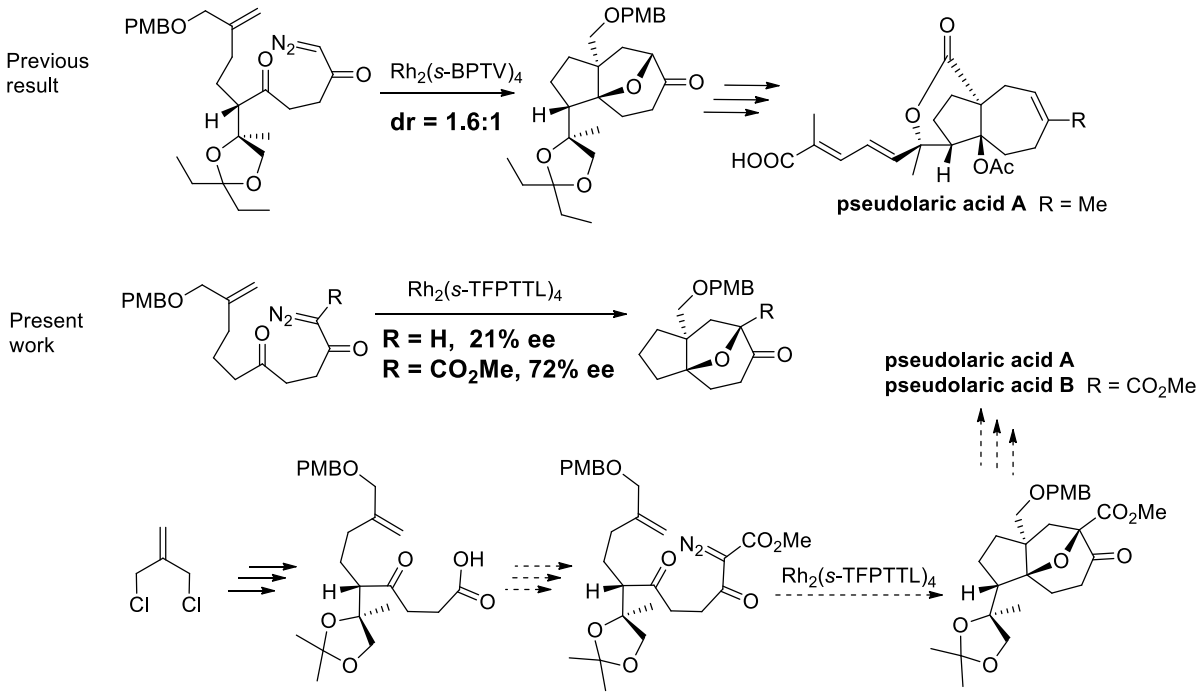

Pseudolaric acids A and B are the main biologically active constituents of *tujingpi*, a traditional Chinese herbal medicine for the treatment of dermatological fungal infections. In the past few years, they have enjoyed a resurgence of interest because of the identification of diverse biological activities, such as antimicrobial activity, anti-fertility, cytotoxicity towards cancer cell lines, anti-angiogenic activity, and inhibition of tubulin polymerization.[1]

Our group has reported the first total synthesis of pseudolaric acid A.[2] However, the key step of the carbene cyclization cycloaddition cascade (CCCC) reaction does not give an ideal result, in which the dr of the reaction is only 1.6:1. The CCCC reaction can be understood on the basis of frontier molecular orbital energies. An additional carbonyl group (such as CO_2Me) will reduce the energy level of LUMO (dipole) orbital, thus the energy gap between the LUMO (dipole) and the HOMO (dipolarophile) is decreased.[3] The interaction should be energetically more favourable and the dr value is anticipated to improve. With modified electronic properties or substrates, alternative Rh(II) catalysts to promote the reaction were examined. We will report on our progress in a model study and improved second generation strategy toward the total synthesis of pseudolaric acids A and B.

References

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