Acylphloroglucinols from *Callistemon lanceolatus* DC.

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Asymmetric total synthesis of polycyclic xanthenes and discovery of a WalK activator active against MRSA

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The development of new antibiotics continues to pose challenges, particularly considering the growing threat of multidrug-resistant *Staphylococcus aureus*. Structurally diverse natural products provide a promising source of antibiotics. Herein, we outline a concise approach for the collective asymmetric total synthesis of polycyclic xanthene myrtucommulone D and five related congeners. The strategy involves rapid assembly of the challenging benzopyrano[2,3-a]xanthene core, highly diastereoselective establishment of three contiguous stereocenters through a *retro*-hemiketalization/double Michael cascade reaction, and a Mitsunobu-mediated chiral resolution approach with high optical purity and broad substrate scope. Quantum mechanical calculations provide insight into stereoselective construction mechanism of the three contiguous stereocenters. Additionally, this work leads to the discovery of an antibacterial agent against both drug-sensitive and drug-resistant *S. aureus*. This compound operates through a unique mechanism that promotes bacterial autolysis by activating the two-component sensory histidine kinase WalK. Our research holds potential for future antibacterial drug development.

The emergence of multidrug-resistant bacteria, specifically methicillin-resistant *Staphylococcus aureus* (MRSA), is recognized as a serious threat to public health[1,2]. For example, there were 323,700 cases and 106,00 deaths attributed to MRSA infections in the United States in 2017, resulting in nearly $1.7 billion in associated healthcare costs[3]. However, antibiotic resistance continues to rise, including resistance to vancomycin, daptomycin, and linezolid[4–6]. Therefore, the development of new antibacterial agents is of utmost urgency. A major focus of current antibiotic development is screening based on natural products[7–9]. Xanthenes are an important class of heterocyclic compounds in drug discovery and organic synthetic chemistry because of their broad range of biological activities, particularly their antibacterial activity[10–13], and diverse complex scaffolds. In recent years, xanthenes have attracted significant interest from the synthetic chemistry community, including groups such as Jauch[14], Ready[15], Siegel[16], Porco Jr[17], Martin[18], Pronin[19], Suzuki[20], and Gao[21]. To date, hundreds of xanthenes have been identified in nature[22–25]. As a paradigm, (+)-myrtucommulone D (**1**) (Fig. 1a) is an unusual angular benzopyrano[2, 3-a]xanthene

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