Novel Chiral Aryltetraline Lactone Core And Furo[3,4-C] Pyranone Structure For The Synthesis Of Bioactive Lignans And Furopyranones

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Natural products are the primary source of drugs in clinical use today for various diseases including cancer. Lignans constitute a big group of bioactive natural products with anti-viral, anti-bacterial, anti-inflammatory, anti-parasitic and anti-cancer activities. Aryltetraline lignans such as deoxypodophyllotoxin (DPT) are potent anti-viral, antibacterial, and anticancer compounds. Efficacy of these lignans and their derivatives is attributed to the unique stereochemistry around the polycyclic core, but this core is challenging to synthesize. We found in previous work that the number of steps in the synthesis of the core can be significantly reduced by using an intramolecular styryl Diels Alder (ISDA) reaction, but our previous substrates were not stereoselective. In this work, we have remedied this by synthesizing novel chiral substrates from readily available materials which feature activated dienophiles tethered to the styryl moiety by an ester group. Cyclization of the substrates presenting an activated alkynyl dienophile produces the polycyclic core of arylteraline lactone lignans in yields of 32-70%. Alternatively, doubly activated alkenyl dienophiles produce the furo[3,4-c] pyranone ring structure in 30-70% yields and 5:1 stereoselectivity. We are investigating the mechanisms responsible for the different products. Crystal structures of these novel substrates have been obtained with R value in the range of 0.03-0.04. Here, we will discuss the synthesis, crystals structures, and mechanistic studies of these important structures. These results demonstrate the potential of the asymmetric ISDA reaction in total synthesis of bioactive lignans and furopyranones.

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