Total Syntheses of Polygalolides A and B

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Polygalolides A and B were isolated by Wei and co-workers in 2003 from *Polygala fallax* Hemsl., a medicinal plant used as a tonics and antihepatistis drug in China. The unique structural characteristics of these molecules stimulated our interest as synthetic targets. Herein, we report the first total syntheses of polygalolides A and B that take advantage of a carbonyl ylide cycloaddition strategy.

The carbonyl ylide precursor was synthesized in 15 steps from the known alcohol, readily available from D-arabinose. After considerable experimentation with regard to the key cycloaddition reaction, it was found that dropwise addition of the α-diazoketone to a solution of catalytic amounts of $Rh_2(OAc)_4$ in refluxing benzotrifluoride afforded the desired cycloadduct as a single isomer in 73% yield. The cycloadduct was uneventfully transformed to a tetracyclic lactone through a five-step sequence. Installation of the aromatic moiety could be accomplished by exploiting a Mukaiyama aldol-type reaction between a silyl enol ether and a dimethyl acetal, and β-elimination and deprotection completed the total syntheses of polygalolides A and B. The synthetic materials proved to be identical in all respects to the natural products except for their specific rotations, which were equal in sign but the magnitude was inconsistent with the reported data. A striking difference between them suggests that polygalolides would be biosynthesized in nearly racemic forms.