Total Synthesis of Salviachinensine A Using a Matteson Homologation Approach

[Introduction]
Salviachinensine A was isolated from the Chinese medicinal plant Salvia chinensis by Liu and Cao et al. in 2018. The group of natural products belongs to the family of phenolic acids and are thus derived from Caffeic acid. Salviachinensine A displayed promising antiproliferative activity against the human acute myeloid leukemia cell lines MOLM-13 and MOLM-14 (IC_{50}: 2.3 and 73 μM), while also inducing apoptosis for MOLM-13 at 5 μM.

This activity inspired us to develop the first total synthesis of salviachinensine A. The Matteson reaction was employed as the preferred method for the synthesis of the backbone of the Caffeic acid derivative, as it allowed the successive formation of the stereogenic centers of the lactone moiety.

[The Matteson Reaction] combines the homologation of boric esters to the corresponding α-chloro boric esters and the subsequent introduction of a nucleophile. The carbonoid (L)ClCH serves as the carbon-bearing reagent for the homologation and is generated in situ by deprotonation of dichloromethane with n-butyllithium. Using a chiral auxiliary and zinc chloride both steps proceed with high diastereoselectivity, reaching diastereomic ratios of up to 100:1. A plethora of nucleophiles like organolithium or Grignard reagents, alkoxides and azides can be introduced. The Matteson reaction was utilized for the synthesis of various fragments of natural products due to the modular nature of this method.[23]

[The Total Synthesis] started by esterification of the aryl boric acid with the chiral auxiliary (RR)-dicyclohexyl methane-1,2-diol. The α-chloro boric esters resulting from the homologation of arylboronic esters are prone to epimerization and decomposition, hence the temperature of the reaction mixture should be closely monitored. In this case the temperature should not exceed –40 °C and it is crucial that the α-chloro boric ester is not worked up but instead directly reacted with the nucleophile in a one-pot protocol. Like this, the substituted boric ester was obtained in high yields and diastereoselectivity. While the introduction of the alkoxide nucleophile after the second homologation was relatively sluggish, the α-hydroxy Grignard reagent readily substituted the α-chloro boric ester resulting from the third homologation. It is noted that a higher concentration of the Grignard reagent significantly increased the yield.

[The Cyclization] of the backbone was performed after the oxidation of the boric ester to the respective alcohol. The cleavage of all protecting groups as well as the formation of the carbocation for a Friedel-Crafts alkylation should proceed with Brønsted acid. Both lactonization and Friedel-Crafts alkylation occurred within 10 minutes after treatment with trifluoroacetic acid, though the lactonization probably occurred first, directing the ring closure in a highly diastereoselective manner. For the last step both methylene acetals were cleaved with Lewis acid. It was mandatory to use anhydrous and degassed solvents as the catechol moieties are likely readily oxidized, indicated by the various colors displayed during and after the reaction.

[References]