Asymmetric Synthesis of the Spiro-isoxazoline Natural Products

The bromotyrosine-derived spiroisoxazolines represent a structurally diverse class of physiologically active natural products. The family contains a number of structural types, including monomeric and dimeric compounds (cf. 1-6, Figure 1). A prominent feature is the dibromo spiroisoxazoline amide core with \( R \) or \( S \) absolute stereochemistry of the spiro stereogenic center. Diversity also arises from the spacer diamine linking two dibromo-spiroisoxazoline cores in case of dimeric natural products. Interestingly, 11-hydroxyaerothionin has been shown to inhibit \( M. tuberculosis \) which may be related to inhibition of the mycothiol dependent detoxification enzyme mycothiol S-conjugate amidase (MCA). MSH is a low molecular weight thiol found in actinomycetes such as \( M. tuberculosis \) which plays an important role in detoxification of thiol-reactive substances.

**Figure 1. Monomeric and Dimeric Spiroisoxazoline Natural Products**

Our first target in this series of compounds was the epoxy ketone-containing compound (-)-calafianin. The synthesis of a (-)-calafianin core precursor was initiated by enantioselective tartrate-mediated nucleophilic epoxidation of the readily available quinone monoketal 7 (Scheme 1). We next considered methylation of epoxy ketone 8 to prepare the exocyclic vinyl epoxide 9. An optimal condition was found for olefination employing KOtBu as base and methyltriphenylphosphonium bromide (THF, 0.03 M, \(-40^\circ\)C). This
method was found to be practical for production of gram quantities of key intermediate 9.

We next explored 1, 3-dipolar cycloaddition of vinyl epoxide 9 for spiroisoxazoline construction. Dipolar cycloaddition using a nitrile oxide generated in situ from ethyl chloro oximinoacetate 10 and Zr(OtBu)₄ led to optimal conversion, affording a moderate to high yield (85-93%) of 11/12 (dr = 1.0:1.8) and minimal formation of the furoxan dimer. Key NOE enhancements were observed between diagnostic protons (cf. Scheme 1) to enable assignment of the syn and anti spiroisoxazoline diastereomers.

Scheme 1. Asymmetric Synthesis of (-)-calafianin

The synthesis of calafianin commenced with an extrapolation of the ester–amide exchange methodology. Gratifyingly, after extensive screening of metal additives, we found that addition of Zn(OTf)₂ (20 mol %) in addition to Zr(IV)-2-HYP afforded increased yields of acetal-protected calafianin 13. Late stage acetal deprotection was performed by using 48% aqueous HF in a binary solvent mixture of CH₃CN and CH₂Cl₂ effecting clean hydrolysis of both cyclic kets to afford (-)-calafianin 14 in high yield and purity with negligible hydrolysis and side reactions observed.¹ Similar synthetic route was extended for the synthesis of natural (+)-calafianin and stereochemical determination.