ABSTRACT

The zoanthamine family of alkaloids has attracted the attention of synthetic chemists for over two decades, beginning with the first report of their isolation in 1984. Not only are these stereochemically dense polycyclic compounds structurally fascinating, but they also display interesting and important biological activities. Foremost among these is the potent anti-osteoporotic effect of norzoanthamine. To date, norzoanthamine remains the only member to have succumbed to total synthesis, by Miyashita and coworkers in 2004. Our studies began by targeting zoanthenol, a structurally similar natural product that possesses the key stereochemical challenges of norzoanthamine, while offering unique opportunities for strategic development as compared to the other family members.

The synthetic work described herein focuses on approaches to the tricyclic core of zoanthenol, specifically employing an approach by which the stereochemical complexity of the C ring, marked by the challenging vicinal all-carbon quaternary centers, is addressed early in the synthesis. These functionalized C ring synthons are then tethered to an aromatic A ring synthon, and methods to form the final bond of the B ring are explored. Special attention is given to the acid-mediated Friedel-Crafts cyclization approach. In addition to the acid-mediated cyclization approach, an alternative cyclization method is discussed wherein the A ring is substituted with a halogen in order to enable generation of a radical. This radical then undergoes a 1,4-addition into a fully substituted enone to close the B ring and provide the desired stereochemistry both of the two new stereocenters that are generated in the cyclization.

In these efforts, we have learned a great deal about the factors governing selectivity and reactivity in these systems. For each case, stereochemical models are discussed and key structural requirements for future investigations are outlined.