

## Abstract

This thesis describes the development of new thermal and oxidative radical cyclization methodologies and their application to the total syntheses of alkaloids, particularly to bridged diketopiperazine (DKP) alkaloids.

A practical solvent free approach to diverse DKPs and quinazolines is described. The methodology proceeds by thermal silica gel mediated deprotection of the Boc protecting group and intramolecular condensation of the resulting free dipeptides and tripeptides. It was applied to the total syntheses of alkaloids gyantrypine and ardeemin.

A major part of the thesis concerns with the discovery and applications of novel diketopiperazine derived alkoxyamines. Their propensity to undergo facile thermal C–O bond homolysis to generate captodative DKP radicals and persistent TEMPO radical allowed using them as radical surrogates. The methodology takes advantage of the persistent radical effect (PRE).

The methodology based on PRE was applied in an asymmetric approach to the alkaloid asperparaline C. An asymmetric synthesis of a very advanced precursor to asperparaline C, 8-oxoasperparaline C, was accomplished in 11 steps and 15% overall yield. The key steps of the synthesis include a direct oxidative cyclization of DKPs, regioselective furan dearomatization with singlet oxygen and a reductive radical spirocyclization. The PRE-based methodology was also applied as a conceptually new approach to diverse bridged DKPs. DKPs with widely variable ring sizes were efficiently synthesized. A formal synthesis of antibiotic bicyclomycin was achieved using this methodology.

The DKP derived alkoxyamines display some unusual features. An unusual *trans/cis* isomerization at the anomeric center was discovered and its kinetics were determined by  $^1\text{H}$  NMR spectroscopy. The kinetics of the PRE mediated radical cyclizations were also investigated by  $^1\text{H}$  NMR spectroscopy. These studies provided deep insight into the mechanisms operating in these PRE mediated transformations.