

There has been intense interest in all aspects of penicillin since Alexander Fleming discovered it in 1929. The biosynthetic route to the penicillin and cephalosporin antibiotics starts with three amino acids – L-valine, L-cysteine and L- α -aminoadipic acid. These three amino acids are assembled into the linear tripeptide L- α -aminoadipoyl-L-cysteinyl-D-valine (ACV), which is converted to bicyclic isopenicillin N (IPN), the biosynthetic precursor to all penicillins and cephalosporins, by a single enzyme, Isopenicillin N synthase (IPNS).

IPNS is a non-haem iron oxygenase. The IPNS catalysed reaction is an oxidative cyclisation. The reaction stoichiometry involves the loss of four hydrogen atoms from ACV, concomitant with the reduction of one equivalent of molecular oxygen to two molecules of water. IPNS requires one equivalent of ferrous iron for full activity. IPNS - like the ring expansion enzymes - has been the subject of extensive research interest over many years, because this oxidative bicyclisation reaction is unique in nature and is of key commercial importance.

My project focuses on the synthesis and enzymatic investigations of δ -(L- α -aminoadipoyl)-(3S-methyl)-L-cysteine D- α -hydroxyisovaleryl ester (AmSCOV, 14) and δ -(L- α -aminoadipoyl)-(3R-methyl)-L-cysteine D-S-methyl-cysteine ester (AmCOMC,35) that may allow the trapping and observation of an Fe(II) oxene-containing intermediate in the IPNS system.