COVER FEATURE

Professor Christopher J. Moody *

Recipient of the RSC 2000–2001 Tilden Medal and Lectureship

Career

Chris Moody is a Mancunian and, in between visits to Old Trafford to watch his beloved Manchester United, was educated at Manchester Grammar School. He obtained his BSc from King's College, London, before carrying out his PhD research at the University of Liverpool under the supervision of Charles Rees investigating the synthesis and reactions of nitrogen–sulfur ylides. He spent a postdoctoral year at the ETH in Zürich working with Albert Eschenmoser on the stereochemistry of E2′-elimination reactions before taking up a post in industry at Roche. In 1979 he was appointed to a lectureship at Imperial College, London, renewing his collaboration with Charles Rees in parallel to establishing an independent research career. He was promoted to a readership in 1989, and in 1990 moved to the chair of organic chemistry at Loughborough University. In 1996 he was appointed Professor of Organic Chemistry at the University of Exeter, and in October 2000 took up an EPSRC Senior Research Fellowship.

Moody's work has been recognised with several awards including the RSC Hickinbottom Fellowship and Corday Morgan Medal (both in 1986), the Tilden Medal and Lectureship (2000–2001), and the Adrien Albert Medal and Lectureship (2001).

Research

Moody's research interests are in heterocyclic chemistry, an area of immense importance, given that heterocyclic molecules account for over half of all known compounds. Within this broad area, two themes are apparent in his work: firstly, the development of new reactions for the synthesis of heterocyclic compounds, in particular reactions involving species such as nitrenes or rhodium carbenes, and secondly his work on the synthesis of biologically active heterocycles.

Early work was concerned with reactive intermediates, especially nitrenes. Thus, in collaboration with Charles Rees, he extensively developed the use of nitrene cyclisations, and successfully exploited such reactions in the synthesis of a number of biologically active heterocycles, most notably indoles and their derivatives. Examples of successfully completed syntheses which involve such reactions as a key step include: the coenzyme PQQ,[1] and phosphodiesterase inhibitors PDE-I and -II.[2] Later independent work saw the completion of the synthesis of the alkaloids murrayaquinone-B,[3] lennoxamine,[4] indolactam V[5] and BE10988 (Fig. 1).

In a continuation of interest in reactive intermediates, *ortho*-quinodimethanes were next investigated. These species are usually viewed as useful, but unstable reagents, for organic chemistry. However, the Diels–Alder reactions of stable *ortho*-quinodimethanes based on α-pyrones fused to 5-membered ring heterocycles has been developed as an extremely versatile new route to benzofused heterocycles.[7] Thus syntheses of the antibiotic carbazomycin,[8] and the staurosporine aglycone were both achieved using this chemistry (Fig. 2).[9] His synthesis of

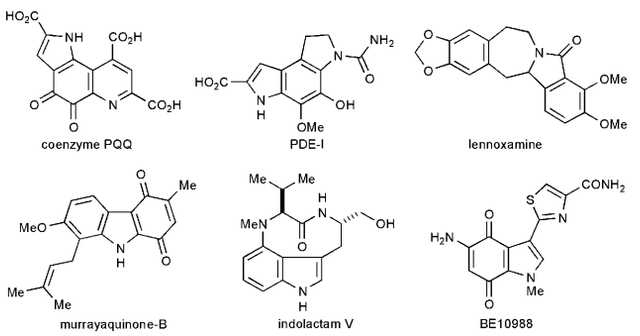

Fig. 1

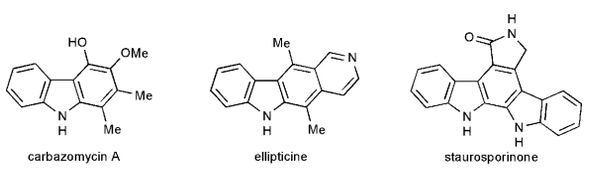

Fig. 2

the anticancer alkaloid ellipticine using this methodology[10] remains the shortest route to this important natural product.

An ongoing theme is the use of rhodium carbenes in synthesis. These reactive intermediates, generated by the action of dirhodium(II) catalysts on diazo compounds, undergo a wide range of synthetically useful reactions, although Moody has largely concentrated on one particular aspect of their chemistry—the so-called X–H insertion reaction (X = O, N, Si). For example, intramolecular O–H insertion reactions were developed as a route to 7- and 8-membered medium ring ethers.[11] The group's studies have not only demonstrated the value of such cyclisation reactions in synthesis, but have also attempted to delineate the factors affecting such carbene insertions and their stereoselectivity.[12] Thus it was found that the metal ligands can have a dramatic effect on the chemical reactivity of the reactive intermediate in, for example, the carbenoid cyclisation to give oxindoles and in the intramolecular Buchner reaction.[13] Recent studies have succeeded in identifying superior catalysts for carbenoid insertion reactions, including asymmetric Si–H insertion reactions using chiral catalysts.[14] These catalysts have also been used for carbenoid N–H insertion reactions in routes to α-amino acid and α-aminophosphonate derivatives,[15] and a highly chemoselective version of this reaction has been developed as a key step in a completely novel approach to the synthesis of peptides.[16]

The N–H insertion reactions described above exhibit extremely high chemoselectivity even in the presence of other potentially reactive sites such as N–H groups and aromatic rings. This has enabled their use in complex situations, and therefore the work has evolved into an interest in the thiopeptide antibiotics, macrocyclic poly-heterocyclic systems containing oxazole, thiazole, indole and pyridine rings. Using novel routes to construct the constituent heterocycles, Moody has completed the synthesis of nostocyclamide,[17] and the first synthesis of the thiopeptide antibiotic promothiocin A (Fig. 3).[18]

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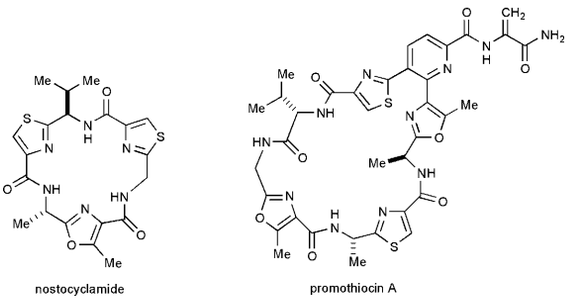

Fig. 3

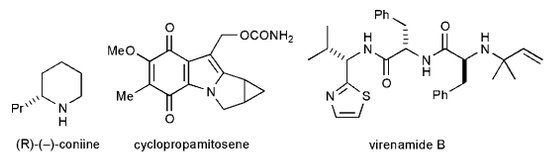

Fig. 4

Current projects include synthetic approaches to diazonamide A and amythiamycin A.

Another research programme is aimed at increasing our understanding of the biological mechanism of action of certain classes of antitumour agents, the so-called bioreductive drugs. The studies are aimed at developing new heterocyclic anticancer agents, and investigating their activation by the various reductases present in tumour cells. Hence, a series of molecules, the indolequinone based cyclopropamitosenes (Fig. 4), has been designed, synthesised, and evaluated.[19] These and other rationally designed quinones exhibit potent biological activity; recent studies have shown that they display excellent specificity for a key enzyme (NQO1) in the bioactivation process, and show the required differential cytotoxicity.[20]

Major current interests in the research group include the use of indium as a reducing agent,[21] and the use of chiral oxime ethers in asymmetric synthesis. This is the first systematic study of such oximes, and has resulted in the development of (*R*/*S*)-*O*-(1-phenylbutyl)hydroxylamine (ROPHY/SOPHY) derived oximes as versatile starting materials for the asymmetric synthesis of a variety of nitrogen containing compounds. Thus, new routes to simple chiral amines have been developed, and extended to the preparation of α-amino acids and their β-amino acid homologues.[22,23] The work has led to the asymmetric synthesis of naturally occurring piperidines such as the hemlock alkaloid coniine,[24] and, by incorporating a ring-closing metathesis after the oxime addition reaction, to a range of 2-substituted 5-, 6- and 7-membered nitrogen heterocycles.[25] An oxime addition reaction was also used as a key step in the synthesis of virenamide B,[26] a cytotoxic thiazole containing peptide, thereby linking this project back to the work on heterocycles and peptides described above.

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