Dr Donald Craig*

Recipient of one of the 1998 RSC Corday–Morgan prizes

PERKIN 1 COVER FEATURE

Career

Donald Craig was born in Richmond, North Yorkshire in 1961 but grew up across the Pennines in Lancaster. He obtained his BSc at Imperial College graduating with First Class Honours in 1983, and stayed on at Imperial to carry out doctoral research in the laboratory of Professor Steve Ley, working on synthetic approaches to limonoid insect antifeedants isolated from the neem tree *Azadirachta indica*. He obtained his PhD in 1986 and then went to Columbia University on an SERC/NATO Fellowship to work on macrocycle-controlled stereoselective epoxidation with Professor Clark Still. He returned to Imperial College in 1987 to take up a lectureship in organic chemistry, and in 1997 was promoted to Reader. He was a visiting professor (*categoría catedrático*) at the University of Salamanca in 1996. When not running his research group of some fifteen coworkers he relaxes playing the blues on his Gibson ES 330, also made in 1961.

He has received several awards in recognition of his contributions, including a Pfizer Academic Award (1994), a ZENECA Award for Research in Organic Chemistry (1994), a Glaxo Wellcome Award for Innovative Organic Chemistry (1996), a NOVARTIS Chemistry Lectureship (1998) and one of the 1998 Royal Society of Chemistry Corday–Morgan prizes.

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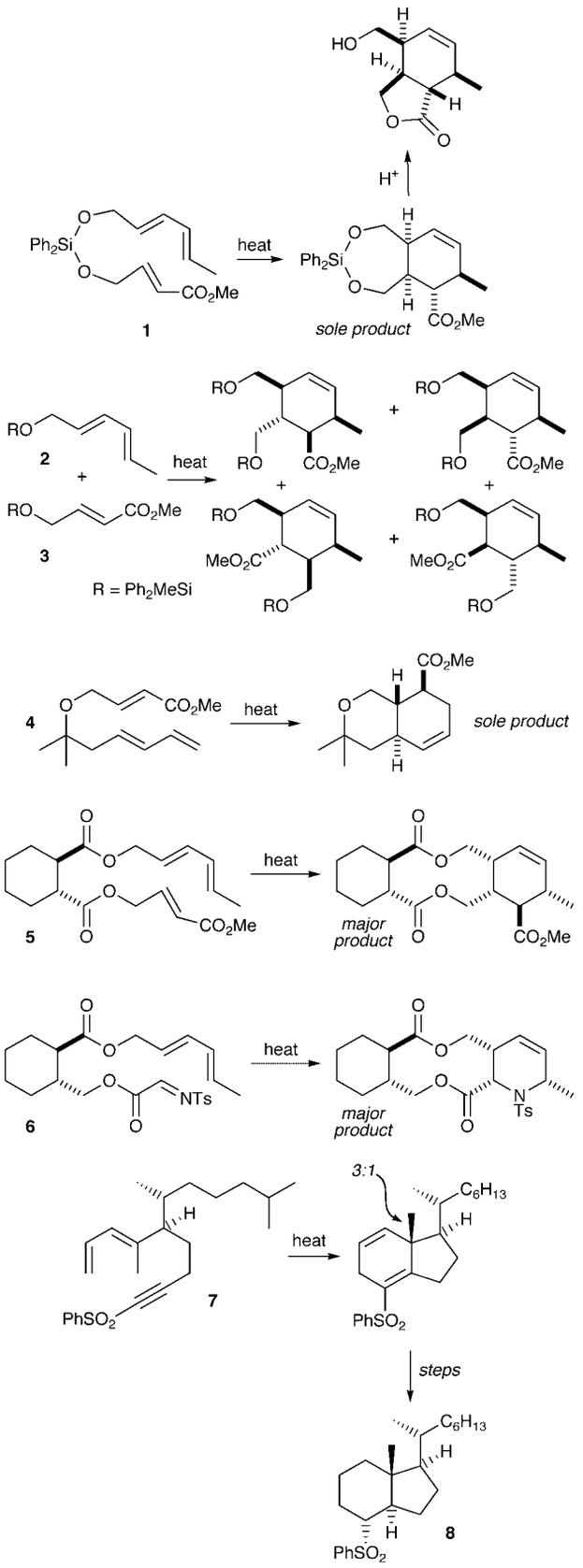
Research

Our research has encompassed a range of topics within the broad areas of synthetic methods and target-oriented synthesis, with particular emphasis on developing an understanding of the factors influencing stereoselectivity in carbon–carbon bond-forming reactions. In addition, the group seeks to demonstrate the utility of its discoveries by applying the new methods to the synthesis of targets of biological interest, especially heterocyclic compounds. Other themes have included the use of temporary, covalent tethers for the control of selectivity in cyclisation and cycloaddition processes; 5-*endo-trig* reactions for tetrahydrofuran and pyrrolidine synthesis; sulfone-mediated heterocyclic synthesis; intramolecular Diels–Alder reactions; *C*-glycosidation reactions; cation-mediated carbon–carbon bond-forming reactions in the context of heterocyclic synthesis; solid-supported organic synthesis.

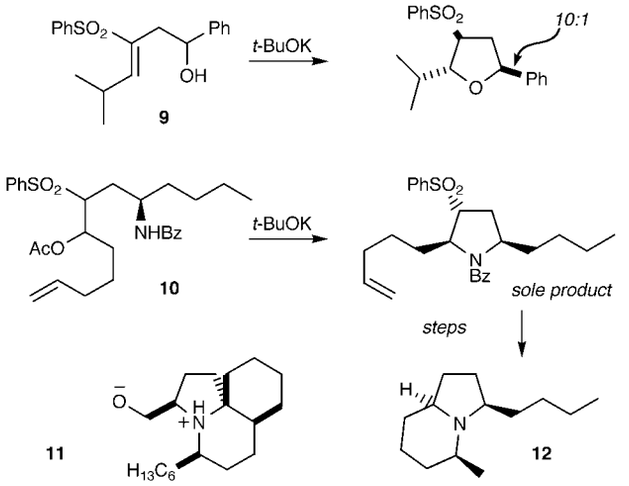
One of our first lines of investigation was concerned with solving problems of poor regio- and stereoselectivity in the Diels–Alder reaction. We developed the use of silaketal tethers to attach the diene and dienophile to each other temporarily. Although the first substrate synthesised (**1**) was poorly reactive it underwent thermal [4+2] cycloaddition with complete regioselectivity and virtually 100% stereoselectivity. Simple acid treatment yielded a single, lactonised product of formal overall intermolecular reaction; significantly, the analogous bimolecular reaction of **2** and **3** yielded non-selectively a mixture of all four possible cycloadducts. More highly substituted second-generation silaketal substrates were markedly more reactive, and their reactions demonstrated complete communication of stereochemistry from stereocentres on the tether carbon atoms to the newly-formed centres in the product cyclohexenes. The work was later extended to trienes with ether linkages such as **4**, and to two new classes of homo- and hetero-Diels–Alder substrates represented by **5** and **6** possessing two ester linkages in the tether, whose cycloadditions gave medium ring-containing products with good stereoselectivity. We have looked also at more conventional intramolecular Diels–Alder strategies for the synthesis of structural sub-units of steroidal natural products. After initial studies had demonstrated low Diels–Alder reactivity of *vinylic* sulfone substrates possessing highly hindered diene moieties we found that the *alkynyl*sulfone **7** underwent facile intramolecular cycloaddition to provide a key intermediate in the synthesis of the vitamin D_3 CD-ring fragment **8**.

Another of our early projects involved the development and utility in natural products synthesis of 5-*endo-trig* reactions of unsaturated sulfones possessing appended oxygen or nitrogen nucleophiles. Although these processes are disfavoured according to Baldwin's guidelines, they may take place readily in the absence of competing alternative pathways. Sulfonyl alcohol **9** underwent cycloisomerisation on treatment with base to give selectively a 2,5-*anti* disubstituted tetrahydrofuran, whilst the secondary benzamide **10** was subjected to a base-mediated

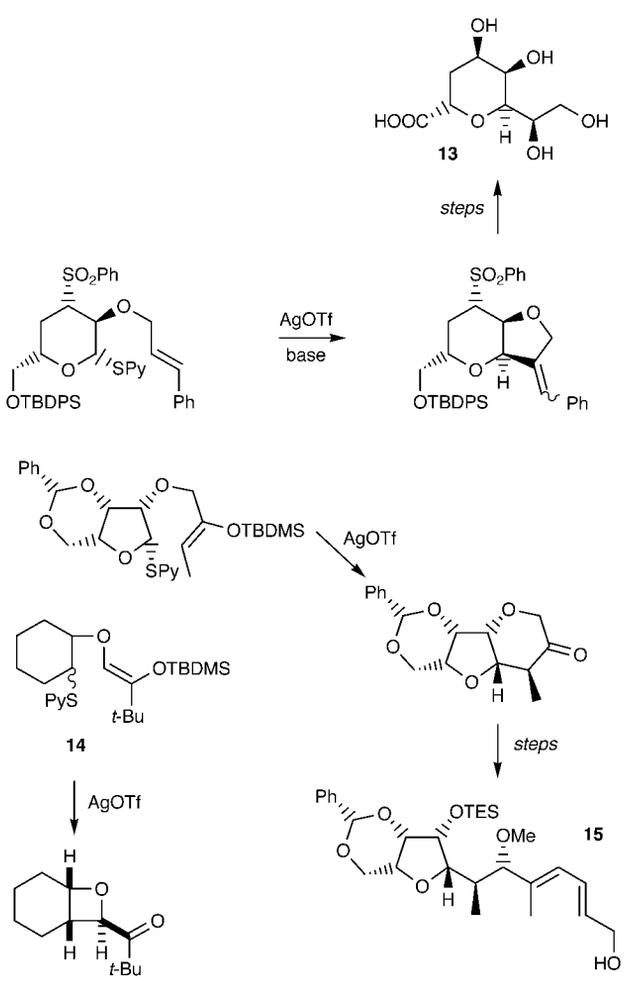


tandem elimination–cyclisation sequence to give an *N*-acylpyrrolidine. Further synthetic elaboration yielded monomorine I (**12**), the trail pheromone of the pharaoh worker ant *Monomorium pharaonis*. Ongoing efforts in this project area are directed towards the synthesis of the potent anti-tumour agent lepadiformine, currently assigned as having the structure **11**.

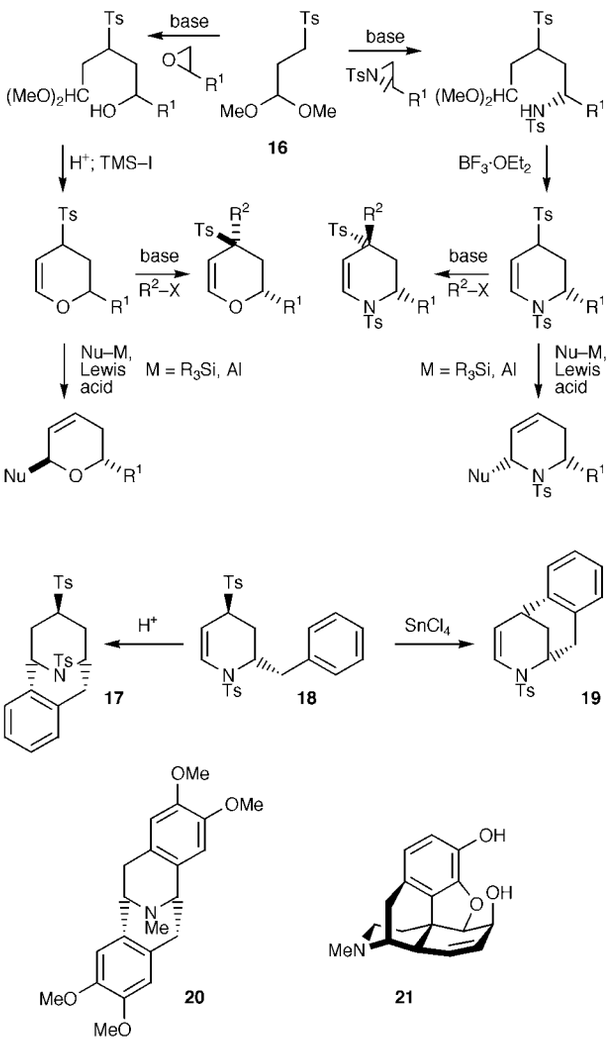
The theme of control of stereochemistry through temporary tethering of reactants has continued in our studies of



C-glycoside synthesis. Covalent attachment of a nucleophilic side-chain to an unprotected hydroxy group in an anomerically activated sugar or analogue gives a cyclisation substrate; ionisation through loss of the anomeric leaving group, cyclisation and cleavage of the covalent tether gives the product of stereoselective formal in*ter*molecular *C*-glycosidation, but with the stereochemical advantages of intramolecularity during C–C bond formation. We have applied this strategy to syntheses of the potent Gram-negative bactericidal higher-order sugar 2-deoxy-KDO (**13**), and of the central portion (**15**) of the elfamycin antibiotic aurodox. A surprising outcome in this area of investigation was the facile oxetane formation observed when anomeric sulfide **14** was treated with a thiophilic Lewis acid.

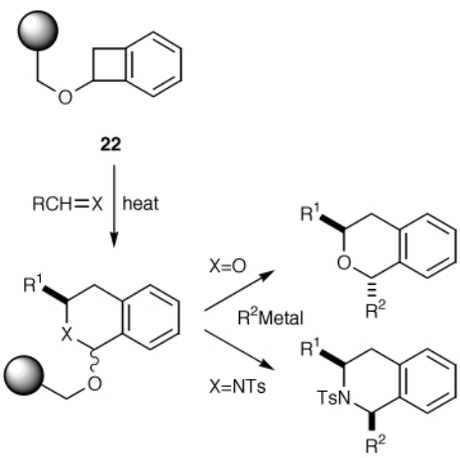


Currently the group is involved in several additional projects in which key intermolecular bond-forming reactions are mediated by cationic intermediates. Two areas of heterocyclic chemistry have been developed concurrently in this context, and again sulfone chemistry plays a major role. Acetal **16** may



be combined with epoxides and activated aziridines under basic conditions to give respectively secondary alcohols and sulfonamides, both of which undergo acid-catalysed cyclisation reactions to provide unsaturated heterocyclic products. The oxygen (glycal) and nitrogen (tetrahydropyridine) analogues showed opposite stereoselectivities in a number of subsequent carbon–carbon bond-forming transformations proceeding *via* anionic and cationic intermediates. Nitrogen congeners possessing additional nucleophilic functionality in the side-chain underwent regiocomplementary cyclisation depending on the nature of the acid employed; on treatment with Brønsted acid, tetrahydropyridine **18** gave **17**, but on exposure to *Lewis* acid **19** was formed. We are seeking to extend and exemplify these findings in syntheses of pavine alkaloids, *e.g.* argemonine (**20**), and of morphine (**21**) and their analogues.

One of the most recent departures in our group is the investigation of traceless linkers and related strategies for solid-phase organic synthesis. Traceless linkers are loosely defined as groups which enable synthesis on polymeric supports in which the cleavage step leaves no vestige in the product of its previous attachment to the polymer phase. We have pioneered the use of polystyrene-supported benzocyclobutenes (**22**) which on thermolysis in the presence of homo- and heterodienophiles give cycloadducts either released directly into solution or still attached to the support. In the latter case, the products may be



cleaved from the support concomitantly with further carbon–carbon bond-forming reactions.

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