Asymmetric Synthesis in the Pursuit of Biologically Important Natural Products

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General Introduction

Our research interests are in synthetic organic chemistry, and the contribution that this science can make to the fields of medicine and natural products. We concentrate on developing new methodologies for synthetic organic chemistry and asymmetric synthesis and then using our chemistry to make biologically important natural products.

Our work is directly relevant to the pharmaceutical industry and the research group is supported by multi-national companies including Merck, AstraZeneca, GlaxoSmithKline, Lily, Novartis, Roche, Aventis and Pfizer. The facilities available for research in our labs in the new building are second to none.

The research group consists of four part II's, eleven DPhil students and six postdoctoral assistants. We meet as a group twice weekly to discuss recent developments in the lab and advances in organic chemistry in general.

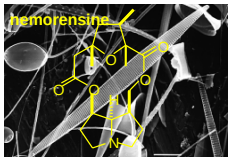
We are an active and vibrant research group; we aim to produce novel methodology and then prove the usefulness of our chemistry in the synthesis of natural products. Our research effort is split into three areas, two of which are controlling the stereoselective oxidation and reduction of organic compounds. A detailed understanding of each area is essential to almost all synthetic efforts.

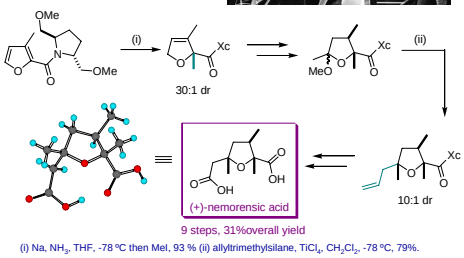
Keywords: ***Asymmetric Synthesis, Natural Products, Oxidation, Reduction, Sugars***

Natural Product Synthesis

We have reported the stereoselective reduction of furans and pyrroles to their dihydro-derivatives.

This methodology has been applied to the synthesis of several natural products including nemorensic acid, secosyrin 1, epi-australine and lactacystein.

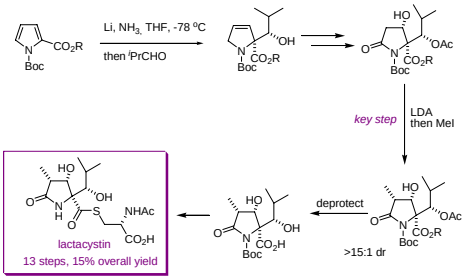




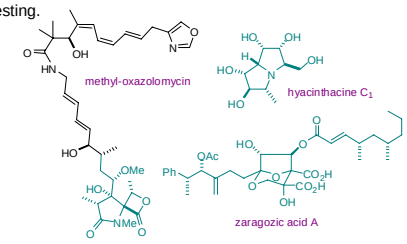
9 steps, 31%overall yield

(i) Na, NH_3, THF, -78 °C then MeI, 93 % (ii) allyltrimethylsilane, $TiCl_4$, CH_2Cl_2, -78 °C, 79%.

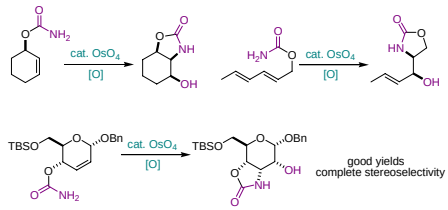
We have reported the synthesis of lactacystin, a neurotrophic growth factor, which has serious potential as a therapy for Alzheimer's disease. The key steps are a Birch reduction of pyrrole and a diastereoslective enolate methylation.



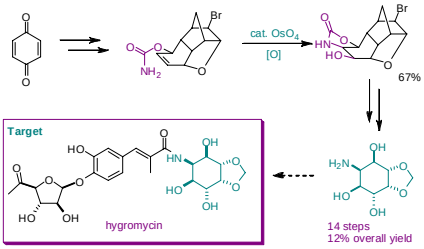
The application of novel chemistry to more complex synthetic targets including oxazolomycin, hyacinthacine C_1 and zaragazoic acid is underway. All of these targets have useful biological activity and we aim to develop short and efficient syntheses which can be used to form analogues for biological testing.



Stereoselective Oxidation



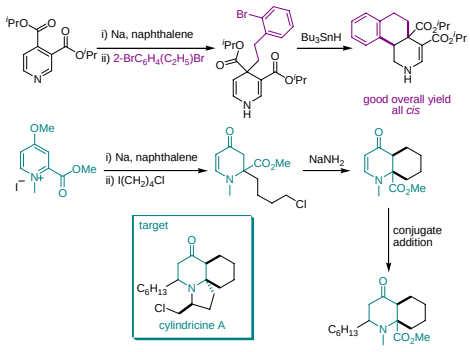
Another area of interest is the controlled hydroxyamination of allylic alcohols and we have been able to control completely the regio- and stereochemistry of this important new oxidation reaction. Application to the synthesis of aminocyclitol antibiotics (such as hygromycin) is in progress.



Partial Reduction

Recently, we began an investigation into the Birch reduction of highly substituted pyridines; this project has reached a really interesting stage and application to the synthesis of biologically important molecules is underway.

In particular, we have been able to use radical cyclisation reactions after the partial reduction process.



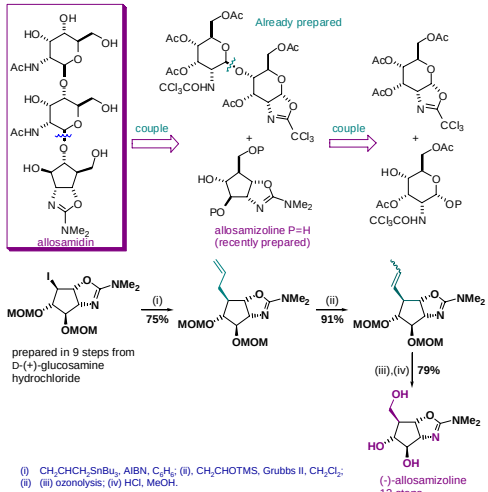
Funding

Our work is directly relevant to the pharmaceutical industry and we are supported *via* several CASE awards with Merck; AstraZeneca, GlaxoSmithKline, Lily, Novartis, Roche and Pfizer. We also have CASE awards with smaller pharmaceutical companies such as The James Black Foundation and Oxford Asymmetry. We also obtain support from the EPSRC and the Leverhulme Trust.

The group's research has been recognised with four prizes: GlaxoWellcome award for innovative chemistry (1998); the Pfizer academic award (2000); the Novartis Young Investigator Award (2001) and the AstraZeneca award (2002).

Sugars

Our interest in sugars derives from our ability to use the Overman rearrangement and controlled oxidation conditions to prepare rare sugars, such as allose and talose. We have recently prepared allosamizoline the aglycone moiety of allosamidin, an important natural product with great potential as an insecticide, whose synthesis is to be completed soon.



(i) $CH_2CHCH_2SnBu_3$, AIBN, C_6H_6; (ii), $CH_2CHOTMS$, Grubbs II, CH_2Cl_2; (ii) (iii) ozonolysis; (iv) HCl, MeOH.

What happens after a Part II or a DPhil?

A Part II or a DPhil in the TJD group will provide a full training In the theory and practical techniques of organic chemistry. As a testament to this, almost all past members of the group have stayed in organic chemistry and have gained jobs with major pharmaceutical companies. Examples are given below.

Part IIs now studying for DPhils in the Donohoe group:

Peter Lindsay-Scott	Katherine Gosby
Jessica Kershaw	Rhian Thomas
Tim O'Riordan	Dave Klauber

Dr M. Waring (PhD, 1996-1999), Dr J. Winter (PhD, 1997-2000) and Dr S. Butterworth (DPhil, 2001-2004) are medicinal organic chemists with AstraZeneca.

Dr. L. Mace (PhD, 1999-2002) Dr. D. House (postdoc, 2000-2002), Dr P. Turner (DPhil, 2002-2005), Dr. R. Harris (DPhil, 2003-2006) and Dr. D. Johnson (DPhil, 2003-2006) are organic chemists with GlaxoSmithKline.

Dr. A. McRiner (PhD, 1997-2000) is a medicinal chemist with Novartis (New Jersey, US).

Dr. A. Calabrese (postdoc, 1999-2001) is a medicinal organic chemist with Pfizer.

Dr D. Carbery (postdoc, 2003-2004) is a lecturer in chemistry at the University of Bath.

References

We publish regularly in all the major journals for organic chemistry and have presented many research seminars and posters at conferences all over the world (e.g. Europe, US, Russia, Australia). Over 90 publications so far: see the following selected references from 2006.

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