**Royal Society of Chemistry Organic Division**
**North East Regional Meeting**
**University of Leeds**
**April 1st 2009**

## Meeting summary

The 2009 North East regional meeting attracted approximately 140 delegates from seven local universities. In addition to talks from Durham, Hull, Leeds, Northumbria, Newcastle, Bradford and York, we enjoyed Keynote Lectures from Prof Sue Gibson (Imperial College London) and Prof Rainer Herges (University of Kiel). Delegates from five of the participating universities also presented over fifty posters. Poster judges from York, Leeds, Durham, Newcastle, and Sanofi-Aventis awarded prizes for the best three posters (1st Miss Angela Kinnell, University of Leeds; runners-up: Mr George Preston, University of Leeds and Mr Anthony Atkin, University of York). A Prize was also awarded for the best student/post doc oral presentation (Dr Joachim Horn, University of Leeds). RSC Publishing donated two annual subscriptions for *Chemical Communications* to the poster and presentation winners. The final program and poster abstract book is appended to this report.

## Financial Statement

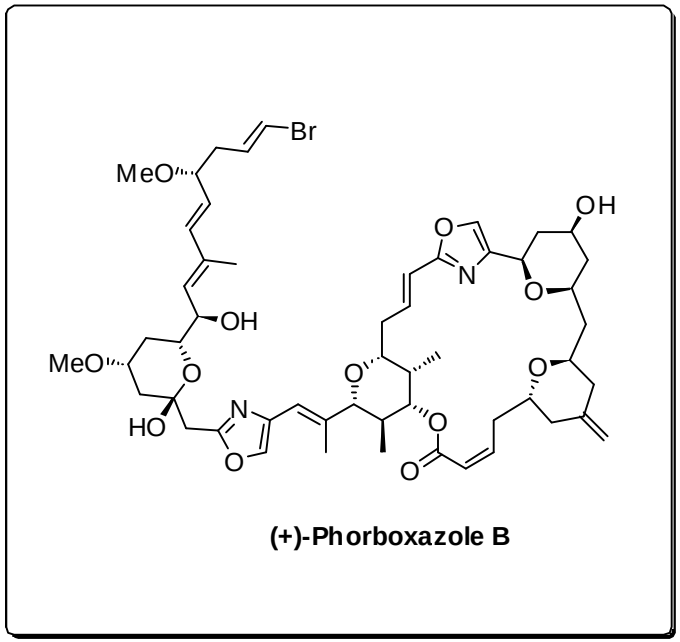
| **Expenditure** | | **Income from sponsorship** | |
|---|---|---|---|
| **Delegate hospitality (140 covers)** | | **Royal Society of Chemistry** | 2000 |
| coffee on arrival | 192 | | |
| lunch | 1024 | **GlaxoSmithKline** | 700 |
| afternoon tea | 255 | | |
| wine reception | 249 | **Syngenta** | 300 |
| **Speakers' travel/hospitality** | | **AstraZeneca** | 200 |
| Prof Rainer Herges (Kiel-Leeds) | 447 | | |
| Other speaker travel expenses | 129 | | |
| hotels | 280 | | |
| dinner for speakers and organisers | 237 | | |
| **Other costs** | | | |
| poster/talk prizes | 250 | | |
| Poster board expenses | 140 | | |
| **Total** | **3203** | | **3200** |

RSC | Advancing the Chemical Sciences

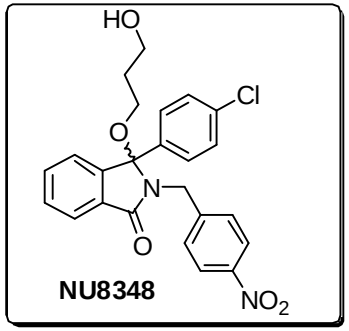
UNIVERSITY OF LEEDS

# *Royal Society of Chemistry*
# *North Eastern Regional Organic Chemistry Meeting*

## *University of Leeds, School of Chemistry*
## *April 1st 2009*




**(+)-Phorboxazole B**

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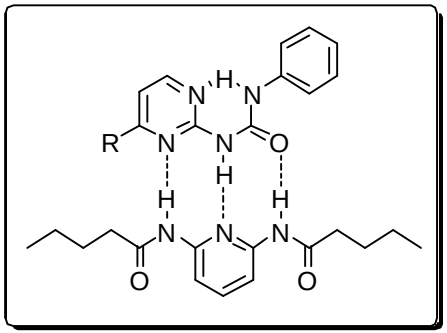


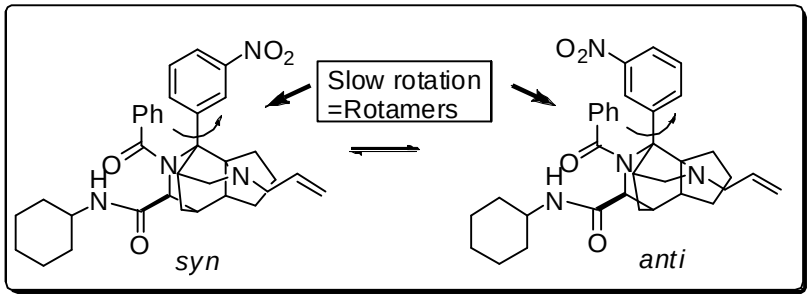

## *Welcome*

The organisers would like to extend a warm welcome you all to for The RSC North Eastern Regional Organic Chemistry annual takes place at the School of Chemistry, University of Leeds on Wedndsday 1st April 2009. We hope that the meeting will be an exciting day to showcase and discuss organic chemistry in its broadest sense within the region and for Postdocs and Students to win some great prizes!!!

Dr Burce Turnbull
Dr Mike Webb
Dr Andy Wilson

The organising committee are grateful to the following orgnaisations for sponsorship of this meeting:

## *Meeting Notes*

The Lectures will take palce in Lecture Theatre A (Please turn of your mobile phones)

The Poster Session will take place in the Chaston Chapman Area

Lunch and Coffees/ tea will be made available in the Chaston Chapman Area

In the Event of a fire alarm please exit the building by the enarest exit under direction of the University of Leeds Staff and congregate on the grass behind the School of chemistry

## *Royal Society of Chemistry North Eastern Regional Organic Chemistry Meeting*

### *April 1st 2009*

### *Final Program*

10.00 Tea/ Coffee

**Session 1 (Chair: Dr Bruce Turnbull, University of Leeds)**

10.30 Prof Sue Gibson (Imperial College London) Cyclisation of Enynes

11.30 Dr Andy Whiting (Durham) Clean, Green and Asymmetric: New Bifuncitonal Catalysts Based on Aminoboronic Acids

11.55 Mr Elliot Coulbeck (Hull) Parallel Kinetic Resolution of Racemic Alcohols

12.20 Lunch and Posters

**Session 2 (Chair: Dr Mike Webb, University of Leeds)**

14.00 Prof Steven Stanforth (Northumbria)

14.25 Dr Andrew Humphrey (Bradford) Novel CMP-Sialic Acid Mimetics Based ona Quinic Acid Skeleton

14.50 Dr Celine Cano (Newcastle) Development of potent inhibitors of the DNA-dependent protein kinase (DNA-PK)

15.15 Dr Joachim Horn (Leeds) The Linchpin Strategy in the Array Synthesis of Diverse Bioactive Ligand Scaffolds

15.40 Coffee/ Tea

**Session 1 (Chair: Dr Andy Wilson, University of Leeds)**

16.00 Poster and talk prizes

16.05 Dr Avtar Matharu (York) Thiophene-based holographic data storage materials

16.30 Prof Rainer Herges (Kiel)

17.30 Wine and Posters

# Cyclisation of Enynes

***Professor Sue Gibson***

Department of Chemistry, Imperial College London, London SW7 2AZ
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**Abstract**

The transition metal catalysed cyclisation of enynes has attracted considerable attention in recent years as the transformation of a relatively simple substrate into a more complex product under catalytic conditions without the generation of byproducts means that reactions of this type fulfil many of the demanding criteria now expected in organic chemistry. This lecture will discuss a study of an asymmetric catalytic enyne cyclisation that incorporates carbon monoxide (an asymmetric catalytic Pauson-Khand reaction), and will present initial results obtained with other metal-catalysed enyne cyclisations using a bis-phosphonate substituted enyne.

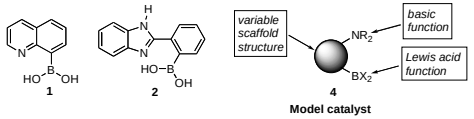


# Clean, green and asymmetric: new bifunctional catalysts based on aminoboronic acids.

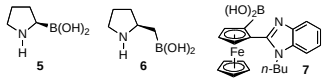
***Andy Whiting***

Department of Chemistry, Durham University, Science Laboratories, South Road, Durham, DH1 3LE, UK.
Email: andy.whiting@durham.ac.uk

Letsinger showed[1] that amino-boronic acid systems **1** and **2** are capable of cooperative catalytic effects, through both the aromatic nitrogen and boronic acid functions. We have become involved the design and development of new, clean, green, efficient catalysts for a range of reactions based upon amino-boronic acids.[2]




We discuss the design and synthesis of novel catalytic amino-boronate systems, such as **5** to **7**, using both asymmetric directed metallation and chiral auxiliary-based approaches. The solid-state and solution structures of these types of systems has also been examined, particularly as a function of pH, and we have used these types of compounds for a range of useful synthetic reactions, particularly in water or under water tolerant conditions. These include the direct amide formation[3] and aldol[4] reaction.



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1. a) R. L. Letsinger and S. H. Dandegaonker, *J. Am. Chem. Soc.*, 1959, **81**, 498; b) R. l. Letsinger and D. B. MacLean, *J. Am. Chem. Soc.*, 1963, **85**, 2230.
2. a) S. W. Coghlan R. L. Giles, J. A. K. Howard, M. R. Probert G. E. Smith and A. Whiting *J. Organomet. Chem.*, 2005, **690**, 4784; b) A. J. Blatch, O. V. Chetina, J. A. K. Howard, L. G. F. Patrick, C. A. Smethurst and A. Whiting, *Org. Biomol. Chem.*, 2006, **4**, 3297.
3. a) K. Arnold, B. Davies, R. L. Giles, C. Grosjean, G.E. Smith and A. Whiting, Adv. Synth, Cat*al.*, 2006, **348**, 813; b) K. Arnold, A. S. Batsanov, B. Davies and A. Whiting, *Green Chem.*, 2008, **10**, 124; c) K. Arnold, B. Davies, D. Hérault and A. Whiting, *Angew. Chem.*, 2008, **47**, 2673.
4. a) K. Aelvoet, A. S. Batsanov, A. J. Blatch, L. G. F. Patrick, C. A. Smethurst and A. Whiting, *Angew. Chem.*, 2008, **47**, 768; b) K. Arnold, A. S. Batsanov, B. Davies, C. Grosjean, Thorben Schütz, A. Whiting and K. Zawatzky, *Chem. Commun.*, 2008, 3879.

# Parallel Kinetic Resolution of Racemic Alcohols

***E. Coulbeck*** *and J Eames**

Department of Chemistry, University of Hull, Cottingham Road, Kingston upon Hull, HU6 7RX.
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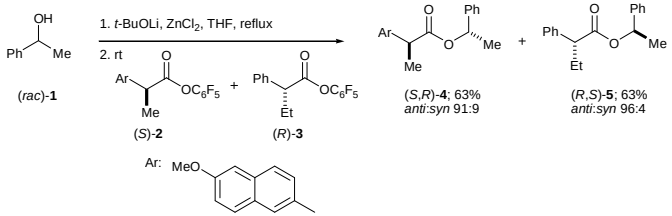
This lecture will discuss the mutual, parallel and kinetic resolution[1] of a series of racemic secondary alcohols[2,3] using a combination of *quasi*-enantiomeric pentafluorophenyl active esters derived from commercially available profens. Using 1-phenylethanol (*rac*)-**1** as our model substrate, we have successfully resolved this by treatment with an equimolar amount of active esters (*S*)-**2** and (*R*)-**3** in the presence of $ZnCl_2$ and lithium *tert*-butoxide in THF at rt (Scheme 1). The levels of mutual stereoselectivity were high (>82% *d.e.*) leading to separable enantiomerically pure ester adducts (*S*,*R*)-**4** and (*R*,*S*)-**5**. Within this lecture, I will discuss the scope and limitation of this methodology and disclose a number of unusual mechanistic features of this reaction, such as solvent effects, temperature and the role of the zinc salt.




**Scheme 1:** Parallel kinetic resolution of 1-phenylethanol (*rac*)-**1** using a combination of *quasi*-enantiomeric active esters (*S*)-**2** and (*R*)-**3**

## References

1. Coulbeck, E.; Eames, J. *Tetrahedron: Asymmetry*, 2008, **19**, 2223-2233.

2. Coulbeck, E.; Eames, J. *Tetrahedron: Asymmetry*, 2007, **18**, 2313-2325.

3. Coulbeck, E.; Eames, J. *Synlett*, 2008, 333-338.



# An expedient synthesis of pyridines, bipyridines and terpyridines

*Prof. Steve Stanforth*

School of Applied Sciences, Northumbria University
Steven.Stanforth@northumbria.ac.uk

**Abstract**

This lecture will discuss an aza Diel-Alder approach to the synthesis of pyridines, bipyridines and terpyridines. Highly substituted heterocycles are available using this methodology. Starting materials are inexpensive and a ‘one-pot’ procedure is available.

O5

# Novel CMP-sialic acid mimetics based on a quinic acid skeleton

***A.J. Humphrey*** *& R.A. Falconer**

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**Abstract**

Sialic acid mimetics have enjoyed a high profile in recent years[1] as anti-influenza drugs and as candidates for treatment of inflammatory diseases and cancers.[1,2] These mimetics typically act by interfering with the binding of sialic acid-recognising (glyco)proteins such as lectins and haemagglutinins, or as inhibitors of key sialyltransferases.

At the Institute of Cancer Therapeutics (ICT), we have developed sialoside and CMP-sialic acid analogues which are hydrolytically stable relative to the parent sialosides. In the course of this work we have investigated replacement of the sialic acid moiety with a carbocyclic (quinic acid-derived) core. Functionalisation of the relatively unreactive 1-OH position can be realised from the quinic lactone-acetonide **1** giving rise to a range of structures as shown below. Alkylation of 1-OH can be used to obtain CMP-sialic acid analogues either *via* direct attachment of a suitably 5'-activated cytidine analogue, or *via* propargylation generating a substrate for a "click" reaction. Free radical deoxygenation or allylation of C-1 using conditions based on the Barton-McCombie reaction[3] is also possible; the product of the former is easily ring opened to an enolisable intermediate with potential for further elaboration at the usually unreactive C-1 carbon. Novel products of these transformations are being used in the development of inhibitors of sialyltransferases implicated in tumour progression.

O6

# Development of potent inhibitors of the DNA-dependent protein kinase (DNA-PK)

***C. Cano***,[a] *N. J. Curtin,*[a] *B. T. Golding,*[a] *I. R. Hardcastle,*[a] *J. Bardos,*[b] *G. C. M. Smith,*[b] *R. J. Griffin.*[a]

[a] Northern Institute for Cancer Research, School of Chemistry, Newcastle University, Newcastle upon Tyne, NE1 7RU, UK. [b] KuDOS Pharmaceuticals Ltd, 410 Cambridge Science Park, Milton Rd, Cambridge, CB4 0PE, UK.
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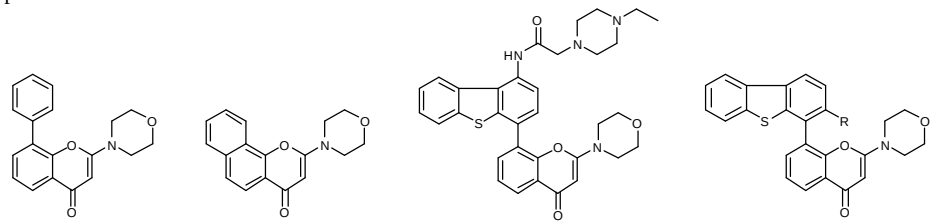
**Abstract**

The cellular response to DNA double-strand break (DSB) formation is an essential component of normal cell survival, following exposure to DNA-damaging chemicals (*e.g.* cisplatin and doxorubicin) and ionising radiation.[1] The serine/threonine kinase DNA-dependent protein kinase (DNA-PK) is a member of the phosphatidylinositol (PI) 3-kinase related kinase (PIKK) family of enzymes, and plays an important role in DNA DSB repair *via* the non-homologous end-joining (NHEJ) pathway.[2] DNA-PK inhibitors may, therefore, be useful as agents to improve the activity of radio- and chemo-therapy in the treatment of cancer.[3] Identification of the lead benzo[*h*]chromen-4-one DNA-PK inhibitor NU7026 ($IC_{50}$ = 0.23 μM), guided the subsequent development of the potent and selective ATP-competitive chromenone NU7441 (DNA-PK $IC_{50}$ = 30 nM).[4] Although proof-of-principle studies with NU7441 confirmed promising activity *in vitro* as a chemo- and radio-potentiator in a range of human tumour cell lines,[5] further biological studies with NU7441 were hampered by sub-optimal pharmaceutical properties.




Structure-activity relationship studies for DNA-PK inhibition by chromenone-derivatives were conducted in conjunction with homology modelling. This approach predicted several positions on the pendant dibenzothiophen-4-yl substituent of NU7441 as tolerant to substitution, without detriment to DNA-PK inhibitory activity. Library synthesis was undertaken employing a solution multiple-parallel approach, by *O*-alkylation or *N*-acylation of the appropriately substituted NU7441 derivatives, respectively, followed by reaction with a range of amines to afford the target compounds. These studies resulted in the identification of compounds that combined potent DNA-PK inhibition with excellent aqueous solubility (20-40 mg/mL as acid salts), without compromising cellular activity. Prominent amongst these derivatives is KU-0060648 (DNA-PK $IC_{50}$ = 8.6 nM), which exhibits 20-1000 fold selectivity for DNA-PK over related PIKK enzymes and PI3K family members.

Interestingly, substitution with a methyl or allyl group (R) at the 3-position of the dibenzothiophen-4-yl ring enabled the separation by chiral hplc of atropisomers, as a consequence of restricted rotation about the dibenzothiophene-chromenone bond, albeit with a marked loss of potency (NU7819, R = 3-Me, $IC_{50}$ = 2.5 μM). The further development of KU-0060648 and analogues will be described.

**References**

1. J. H. J. Hoeijmakers, *Nature*, 2001, **411**, 366.
2 S. P. Jackson, *Carcinogenesis*, 2002, **23**, 687.
3 S. Boulton *et al*., *Carcinogenesis*, 1997, **17**, 2285.
4 I. R. Hardcastle *et al*, *J. Med. Chem.*, 2005, **48**, 7829.
5 Y. Zhao *et al*, *Cancer Res.*, 2006, **66**, 5354.

# The Linchpin Strategy in the Array Synthesis of Diverse Bioactive Ligand Scaffolds

***J.Horn,*** *S.P. Marsden*, A. Nelson**

*School of Chemistry, University of Leeds, Leeds LS2 9JT, U.K., and GlaxoSmithKline, Medicines Research Centre, Gunnels Wood Road, Stevenage SG1 2NY, U.K.*

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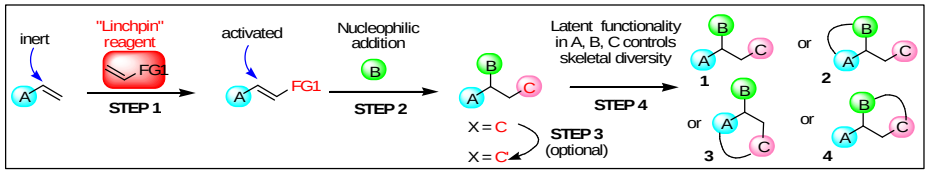
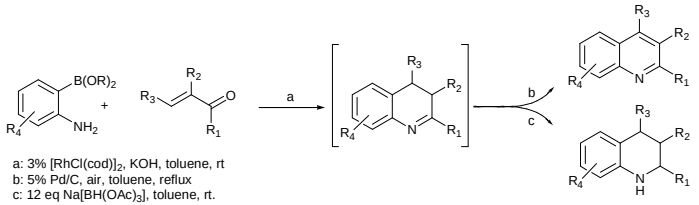
**Abstract**

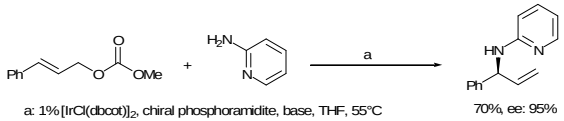
The failure to deliver skeletal or conformational diversity is a major limitation of many existing array technologies, the majority of which focus on the linear assembly of a single structural core and the attachment of various appendages to this core. We wish to report a new approach in which a small number of core units known as "linchpins" facilitate the rapid (and potentially stereoselective) assembly of various building blocks using mutually compatible chemistries. The skeletal and conformational diversity is encoded by latent functional groups appended to each building block: *ie* multiple sites and modes of annulation are possible within a single array design depending upon the substituents and the linchpin chosen (Scheme 1).




The linchpin-activated olefin can be readily transformed by regio- and stereoselective reactions with feedstocks **B** (*eg* boronic acids, amines). The latent functionality in the three substituents, allows for the creation of a final array of compounds. Out of the multitude of methods available for step 2, the rhodium-catalysed asymmetric conjugate addition of boronic acid derivatives[1] was selected as a starting point for studies. Following the project outline closely, this methodology could eventually be applied to a novel quinoline- and tetrahydroquinoline-synthesis, respectively (Scheme 2).[2]




Having thus proved the viability of the original concept, current research deals with the iridium-catalysed $S_N2$ -reaction between substituted amines and allyl carbonates[3] and the application of this transformation to the linchpin strategy (Scheme 3).

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2. J. Horn, S.P. Marsden, A. Nelson, D. House and G.G. Weingarten, *Org. Lett.*, 2008, **10**, 4117-4120.
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# Thiophene-based holographic data storage materials

***A.S. Matharu****

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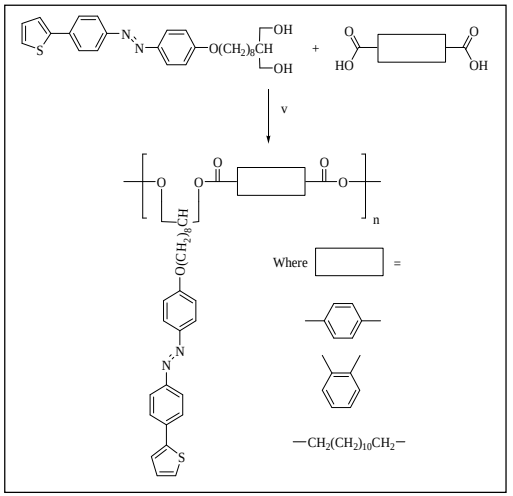
am537@york.ac.uk

**Abstract**

Modern-day society craves for electronic information sending, receiving and storing gigabytes of information on a daily basis. Modern, state-of-the-art storage media such as BluRay DVD is already here effortlessly storing 27 GB. However, such technologies are limited to storing bits of information within a given surface area and dependent on the wavelength of light used. An alternative approach to increasing storage capacity is to consider the entire storage volume of the medium rather that just the surface. This concept is known as holography and offers the potential of storing up to one terabyte of information. Holography data storage is no longer an academic curiosity but is now being commercialised. InPhase Technologies' boast their holographic Tapestry™ media which offers in excess of a staggering 300 GB of storage capacity[1].




As an introduction a brief overview of holographic data storage and liquid crystals will be presented. A rationale leading to the design, synthesis and characterisation of novel side-chain azothiophene-based polyesters for holographic data storage is then discussed.[2,3] The precursor diol exhibits an enantiotropic SmA phase, whereas the final polyesters are amorphous.

The preliminary results show that the polyesters are photoresponsive, with good thermal stability and thick films can be fabricated allowing the potential of multiplexing, *i.e.*, storing several holograms in the same volume. Surface analysis using atomic force microscopy reveals the formation of surface relief gratings

**References**

1. A S Matharu, S Jeeva and P S Ramanujam, *Chem. Soc. Rev.*, 2007, **36**, 1868-1880.
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3. A S Matharu, D Chambers-Asman, S Jeeva, S Hvilsted and P S Ramanujam, *Journal of Materials Chemistry*, 2008, **18**, 3011-3016.

# Aromatics do the twist

***Professor Rainer Herges***

Otto Diels Institute of Organic Chemistry, Christian Albrechts University of Kiel, D-24098 Kiel
rherges@oc.uni-kiel.de

Most of the objects we are dealing with in our every day lives are two-sided. 3-D objects exhibit an inside and an outside surface, 2D objects e.g. ordinary planes have a front and a back side. The twisted Möbius band probably is the simplest and best-known exception.

In the molecular world you need either a molecular band with two edges or a π system to define the twisted topology. Whereas, normal annulenes exhibit two π clouds above and underneath the molecular plane, Möbius annulenes (like Möbius paper strips) only exhibit one periphery with double the circumference. Probably the most striking consequence is the fact that the 4*n*+2 electron count Hückel rule is no longer valid. Magnetic properties and stereochemical features are also peculiar. After our synthesis of the first Möbius annulene in 2003 a number of Möbius extended porphyrins have been prepared and investigated which clearly violate the Hückel rule. Möbius molecules are probably more abundant and less exotic as it was thought before now.

## References

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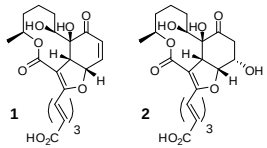
# Synthetic Endeavours Towards the Total Synthesis of the Dictyosphaeric Acids

***Alan R. Burns,[a] Stephen S. Shanahan[b] and Richard J. K. Taylor[a]***
*a) Department of Chemistry, University of York, Heslington, York, YO10 5DD, U. K.*
*b) GlaxoSmithKline, Chemical Development, Old Powder Mills, Tonbridge, Kent, TN11 9AN, U. K.*

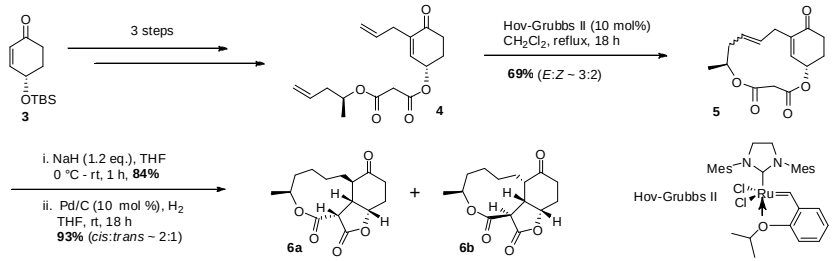
### *1. Introduction*

Dictyosphaeric acids A (**1**) and B (**2**) were isolated from the marine algae *Dictyosphaeria versluyii* in 2004.[1] Dictyosphaeric acid A exhibits antibacterial activity towards Gram-positive bacteria and inhibition of methicillin-resistant *Staphylococcus aureus* (MRSA).[1] On the other hand, dictyosphaeric acid B does not exhibit any significant biological activity.

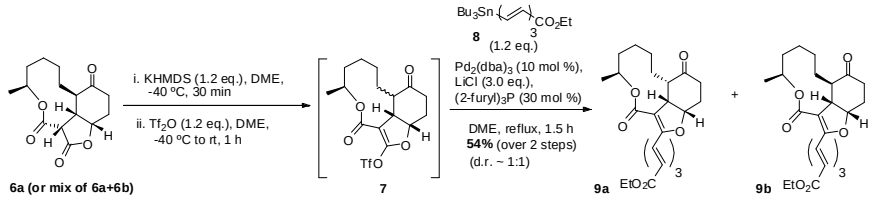



### *2. Synthesis of Tricyclic Core*

Our synthetic endeavours initially focussed on the synthesis of the tricyclic core system **9**. Thus, triene **4** was produced efficiently in 3 steps from known enone **3**.[2]

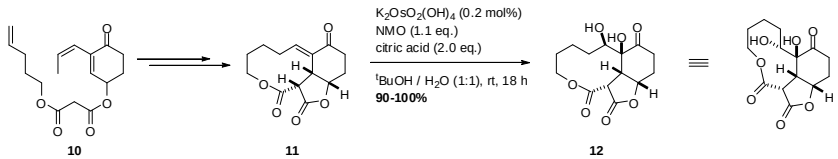



This was elaborated further *via* ring-closing metathesis (RCM), a doubly-tethered intramolecular Michael addition (DTIMA), and hydrogenation to provide fully saturated tricyclic intermediates **6a** and **6b**. Regioselective triflation and Stille coupling followed to furnish tricyclic core, as a 1:1 mixture of diastereomers **9a** and **9b**.[3]




### *3. Current Studies*

Recent work has focused on modifying the above route to allow for introduction of the key diol moiety of the natural products which, subsequently, should then allow for completion of the total synthesis.

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# Photoremovable protecting groups for patterning Self-Assembled Monolayers

***A. S. Achalkumar*[1], *S. N. D. Pradeep* [1], *Panida Prompinit*[2], *Simone Stuart-Cole*[2], *Richard J. Bushby*[1]*, *and Stephen D. Evans*[2]***

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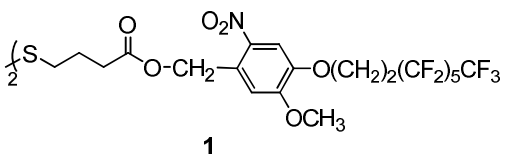
## Abstract

Our ability to accurately pattern photoresists with a resolution down to a few microns has been a key factor in the development of modern electronics. For this purpose various patterning techniques have been developed, like photolithography and electron beam lithography, microcontact printing, and several techniques based on scanning probe microscopy.[1] Among these light is a particularly convenient medium to pattern the surface, as multiple methods for its generation, handling and control are available that exploit different mechanisms of how light interacts with self-assembled monolayers (SAMs). At first sight it would seem that it is a simple extension of known chemistry[2] which provides us with a wealth of photoprotecting groups to chose from, to design the molecules that form the photopatternable SAMs. They are stable under ambient light but can cleave with high quantum yield and high chemical yield using the soft UV (λ = 365nm). However, this protecting group chemistry was optimised for molecules in dilute solution. In a SAM environment the molecules are tightly packed together. Additionally, for SAMs on metal substrates, the ability of the metal to quench the excited state and the fact that it provides a near-by electron source can lead to a very different photochemistry. Nevertheless, the solution photochemistry provides some clues to the problem. For example in the case of ortho-nitrobenzyl derivative (**1**) SAMs, there is a problem of competitive photoreduction against the desired photolysis.[2] This can be solved by modifying the reaction conditions. At the same time we can develop novel photocleavable protecting groups by studying their solution photochemistry. For example, in the case of aryl hydroxylamine we can make use of the photoreduction reaction (homolysis of N-O bond of hydroxylamine) to pattern the aryl hydroxylamine derivative (**2**) SAMs.[3] In essence, this presentation throws light on the contrast between solution and surface photochemistry, and translation of this knowledge in the development of photopatternable SAMs, by taking an example each from the two classes of photocleavable protecting groups described above.



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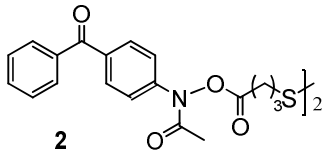

**2**

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3. Manuscript under preparation.



# Studies towards the Total Synthesis of Okaramine B

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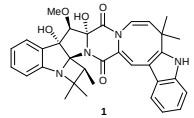
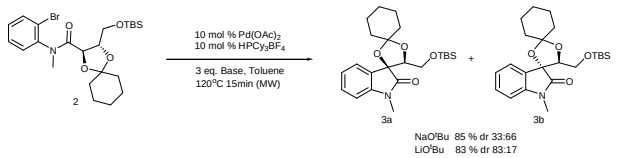
Palladium catalysed α-arylation of amide enolates is fast developing into a general route to chiral oxindoles.[1] 3-Hydroxyoxindoles and derivatives are found in a large number of biologically active compounds. Substrate-directed palladium-catalysed α-arylation has been envisaged as a possible route to these compounds, which would also allow access to highly oxygenated hydroxypyrroloindole skeleta, such as the core of okaramine B.



**1**

Studies on the arylation of tartrate-derived systems have shown the reaction to proceed in good yields, but with modest diastereoselectivity. A base screen showed that the sense of diastereoselectivity can be controlled by switching the counterion of the base from sodium to lithium. Sodium *tert*-butoxide favours the formation of diastereoisomer (**3b**), whereas lithium *tert*-butoxide favours the formation of the opposite diastereoisomer (**3a**). The use of stronger bases, such as lithium hexamethyldisilazide gave improved diastereoselectivity but also lead to a significant decrease in yields.




Despite the modest diastereoselectivity, this methodology was applied to the synthesis of the hydroxypyrroloindole core of okaramine B.

## References

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# Design and Synthesis of Purine-Based CDK Inhibitors

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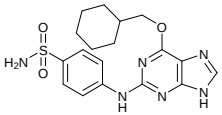
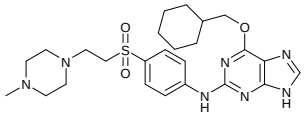
Reversible phosphorylation of protein substrates in the cell is among the most important post-translational modifications ever to occur, and protein kinases play a crucial role in signal transduction pathways in all eukaryotic organisms. Genetic alterations to protein kinases have been demonstrated to lead to a number of diseases including cancer, inflammation, psoriasis and neurological disorders. [1] Cyclin-dependent kinases (CDKs) are a class of serine/threonine protein kinases that play a fundamental role in the regulation of eukaryotic cell-cycle progression, particularly at cell-cycle checkpoints. [2] Cell-cycle alterations result in a loss of cell-cycle checkpoint function, which is associated with an increased CDK activity in human tumours. [3] CDK inhibitors are therefore recognised to have potential therapeutic effects in the treatment of cancer and other proliferative diseases. [4]

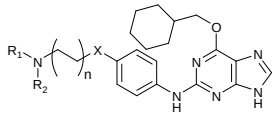
This research project is focused on the synthesis of potent and selective CDK inhibitors based on the purine scaffold. Lead structures derived from previous work undertaken within the research group include NU6102 (**1**) and NU6247 (**2**), the latter of which was chosen as a starting point for the synthesis of a series of compounds (**3**) with potential activity and selectivity for specific members of the CDK family.



**1**
NU6102
$IC_{50}$ = 5 nM (CDK2)



**2**
NU6247
$IC_{50}$ = 120 nM (CDK2)



**3**

**References**

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# Nitrile Hydratases-new thoughts on selectivity

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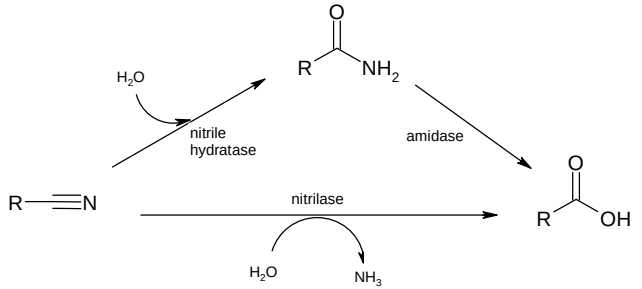
**Abstract**

Nitrile hydratase (NHase) enzymes hydrate nitriles converting them to primary amides without performing any C-N bond hydrolysis to the corresponding carboxylic acid. In this respect, they offer an attractive alternative to chemical methodology which has to be closely controlled to offer the same selectivity. A further advantage to a biocatalytic hydration process is that it avoids the extremes of pH and temperature that are typical with abiotic methodology. The primary sequences of NHases are highly conserved but still fall into two distinct subgroups based around the metal present in the active site which can be either iron or cobalt. Research has been published on the biocatalytic properties of both types with the conclusion that cobalt-centred NHases are more robust and optimized for aromatic nitriles[1] though much work has been published using whole cell preparations of iron-centred NHases for nitrile hydration of aromatic, heterocyclic and alkyl substrates.[2]




One factor that has held up the investigation of NHase as a commonly used biocatalyst has been its availability as a preparation without any residual amidase or nitrilases activity. We have developed a range of NHases which have been produced via recombinant means in *E.coli* from both the iron and cobalt subgroups, using sequence data from a range of microbial genomes. In this poster we will report on the utility of these enzymes for biotransformations which are highly chemo- and regioselective, but also show clear differences in selectivity between the cobalt and iron centred NHases. We will also show preliminary data which will indicate that contrary to previous reports which have linked chiral output from biotransformations using the nitrile-to-acid pathway to highly enantioselective amidases,[3] some NHases do hydrate nitriles highly enantioselectively.

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# Development of Atropisomeric DNA-Dependent Protein Kinase (DNA-PK) Inhibitors

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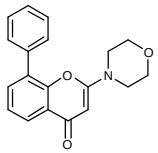
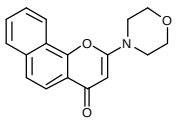
## Abstract

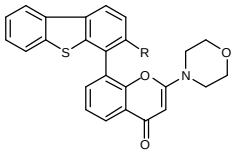
The cellular response to DNA double-strand break (DSB) formation is an essential component of normal cell survival, following exposure to DNA-damaging chemicals (*e.g.* cisplatin and doxorubicin) and ionising radiation.[1] The serine/threonine kinase DNA-dependent protein kinase (DNA-PK) is a member of the phosphatidylinositol (PI) 3-kinase related kinase (PIKK) family of enzymes, and plays an important role in DNA DSB repair *via* the non-homologous end-joining (NHEJ) pathway.[2] DNA-PK inhibitors may, therefore, be useful as agents to improve the activity of radio- and chemo-therapy in the treatment of cancer.[3]



LY294002



NU7026



**NU7441**; R = H
**NU7817**; R = propyl
**NU7818**; R = allyl
**NU7819**; R = Me

In the absence of suitable structural biology information for DNA-PK, inhibitor design has been guided by a combination of structure-activity relationship (SAR) studies and homology modelling, based on the non-selective PIKK inhibitor LY294002. Identification of the lead benzo[*h*]chromen-4-one DNA-PK inhibitor NU7026 ($IC_{50}$ = 0.23 μM), guided the subsequent development of the potent and selective ATP-competitive chromenone NU7441 (DNA-PK $IC_{50}$ = 30 nM).[4] Although proof-of-principle studies with NU7441 confirmed promising activity *in vitro* as a chemo- and radio-potentiator in a range of human tumour cell lines,[5] further biological studies with NU7441 were hampered by sub-optimal pharmaceutical properties. Interestingly, substitution with a propyl, allyl or methyl group (R) at the 3-position of the dibenzothiophen-4-yl ring enabled the separation by chiral hplc of atropisomers, as a consequence of restricted rotation about the dibenzothiophene-chromenone bond.

The development of NU7441 derivatives bearing substituents at the dibenzothiophene 3-position, their resolution using chiral HPLC and their biological evaluation will be described.

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# PROdrugs, Leaving Healthy Cells Alone: Towards Truly Selective Chemotherapy

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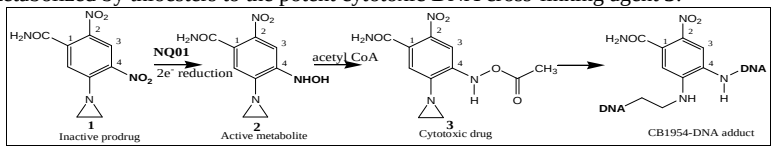
Department of Chemistry, School of Applied Sciences, University of Northumbria, Newcastle, NE2 3RD, UK

## *Background*

Prodrugs are the non-toxic form of a drug which are only converted into their active forms upon metabolism in the body.[1] The prodrug 5-(aziridin-1-yl)-2,4-dinitrobenzamide (CB1954) **1** discovered during the 1950s is effectively reduced (in vivo and in vitro) by the NAD(P)H dehydrogenase; DT-diaphorase (NQ01) enzyme present in certain solid rat tumors[2] to the toxic metabolite **2,** which is further metabolized by thioesters to the potent cytotoxic DNA cross-linking agent **3**.[3]




## *Prodrugs in Chemotherapy*

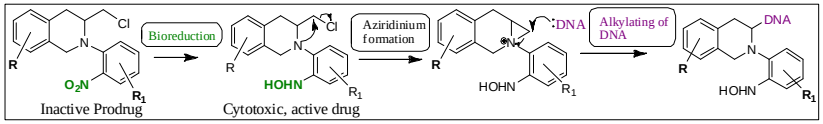
Unfortunately, the human NQ01 enzyme is less effective at reducing CB1954 compared to rat NQ01.[4] Enzymes currently being studied as potential CB1954 activators are the endogeneous NRH: Quinone Oxidoreductase 2[5] (NQ02) enzyme also present in elevated levels in certain solid tumors and the exogeneous Nitroreductase[6] enzymes, as illustrated:

| CB1954 | rNQ01 | hNQ01 | hNQ02* | E. coli Nitroreductase |
|---|---|---|---|---|
| Reduction rate($min^{-1}$) | 4[6] | 0.64[6] | 360[8] | 360[6] |
| Reduction site | 4-nitro | 4-nitro | 4-nitro | 2 and 4-nitro (1:1) |
| Source | rat | human | human | Bacteria *Escherichia coli* |

*when activated[7]

## *Novel Prodrug Designs*

We have developed series of prodrugs containing $NO_2$ groups targeted towards bioreduction. Enzyme turnover rates of these compounds have been promising when tested in vitro, with some surpassing CB1954. We have based the design of our compounds on the **bioactivation** properties of CB1954, and the **cytotoxicity** of the nitrogen mustards which are well known DNA alkylating agents.

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# Application of the Maitland-Japp reaction towards the total synthesis of (+)-Phorboxazole B

Nimesh Mistry[a], Paul A. Clarke[a], and Alexander Humphries[b]

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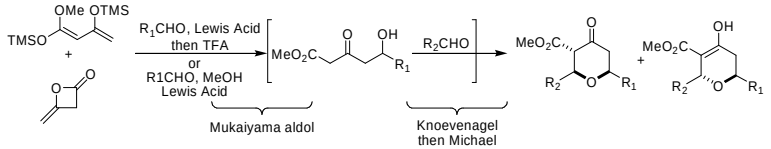
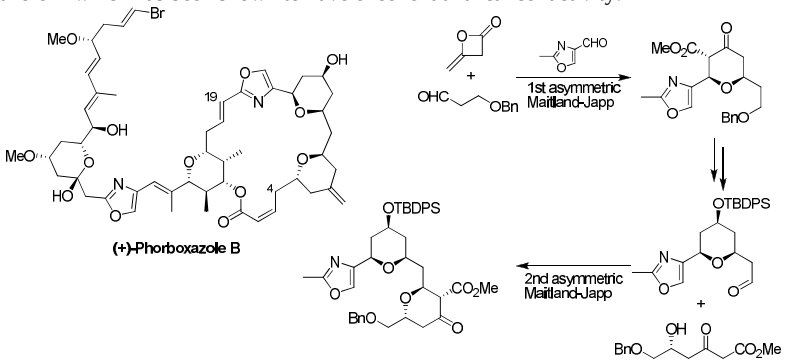
[b]*Astrazeneca R & D, Charnwood, Bakewell Road, Loughborough, LE11, 5RH*

Our group have recently developed an updated version of the Maitland-Japp reaction to synthesise tri-substituted tetrahydropyranones in one-pot and in high yield. [1,2] The methodology can be used to make both 2,6-syn or 2,6-anti tetrahydropyrans with the ratio of the two controlled by the Lewis acid and conditions of the reactions used.




We are currently applying this reaction towards the total synthesis of the marine natural product (+)-Phorboxazole B which has been shown to have excellent anti-cancer activity.[3]




We will present the details of the synthesis of the C4-C19 subunit using the asymmetric Maitland-Japp reaction and our efforts to complete the natural product.

**References**

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# De novo Design and Synthesis of Novel Inhibitors of the Bacterial Mur Enzymes

Katie Simmons University of Leeds Dr C Fishwick and Prof AP Johnson

**Abstract**

The era of antibacterial chemotherapy began in the 1930s with the introduction of the sulfonamides and penicillin. These led to a dramatic decline in the incidence of life-threatening bacterial infections like meningitis and pneumonia.
However, the introduction of a new therapy into the clinic is now shortly followed by the emergence of resistant bacteria. The development of resistance can be viewed as an inevitable consequence to the introduction of new therapies and all antibiotics now have a short, finite lifetime. Increased emergence of pathogenic bacterial strains with high resistance to antibiotic therapy has created an urgent need for the development of new antibacterial agents directed towards novel targets.
In this project, the 3-dimensional structures of the *E. coli* MurA and MurD enzymes and the *S. pneumoniae* MurF enzyme have been used in conjunction with the *de novo* design programme; SPROUT and the vHTS screening programme; eHiTS to identify new classes of Mur enzyme inhibitors. Short and efficient syntheses of these molecules have been developed and these molecules were then screened for enzyme inhibition and whole cell antibacterial activity.
Amongst the potential inhibitors generated, several of the ligands designed to target the MurA enzyme showed excellent inhibitory activity with $IC_{50}$ values of less than 100 μM, some also showed weak antimicrobial activity against both Gram-positive and Gram-negative organisms. These molecules are predicted to bind covalently to the MurA enzyme, in a manner similar to that of the known drug, fosfomycin and are specific to the MurA enzyme.
Several of the ligands designed to target the MurF enzyme also showed moderate inhibition, the best of these exhibiting 39 and 22 % enzyme inhibition at 100 μM respectively.

**P10**

## Design and Application of Novel Brominated Chemical Tags to Facilitate MS Proteome analysis

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srb109@yok.ac.uk

**Abstract**

Chemical tagging of peptides prior to mass spectrometric analysis is often used to simplify and enrich complex mixtures of peptides generated during shotgun proteomics experiments [1]. Chemical tags can target the N-terminus of peptides or be designed to target specific amino acid side chains, such as those on cysteine residues. The tags can also be further developed to incorporate stable isotopes for quantitation of peptides, *e.g.* ICAT™ and iTRAQ™ reagents.

This poster presents the results of our investigations of the synthesis and application of solid-phase bound chemical tags to modify peptides for mass spectrometric analysis, for proteomics applications. As the tags are immobilised onto a solid-phase there is no excess tag present in the reaction once tagging has taken place, and the solid-phase work flow is much simplified compared to solution-phase tagging. The chemical tags used in this work incorporate one bromine atom to act as a mass peak splitter in MS analysis. This allows ready recognition of labelled peptides, which is an advantage when working with samples from a complex biological matrix, which are prone to high background noise.

**References**

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**P11**

## Design, Synthesis and Binding Properties of Conformer Independent Linear Hydrogen-Bonding Arrays

***Adam Gooch***,[a] *Andrea M. McGhee*[a] *Lisa C. Renton*,[a] *Jeffrey Plante*,[a] *Christopher I. Lindsay*,[b] *Andrew J. Wilson**[a,c]

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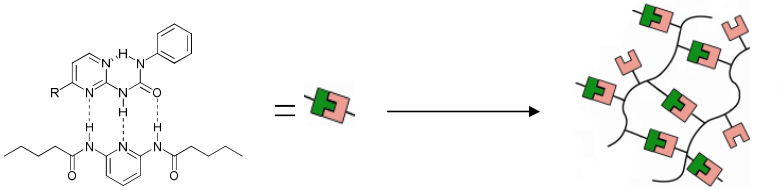
The ready synthetic availability of hydrogen-bonding motifs capable of selective molecular recognition is fundamental to the development of self-assembled materials with stimuli-responsive properties.[1] Designing such motifs is challenging because intramolecular hydrogen-bonding, preorganisation, secondary interactions, tautomerism and electronic substitutent effects all effect the strength and fidelity of association to complementary binding partners.[2] Ureidopyridines are synthetically accessible donor-donor-acceptor (DDA) hydrogen-bonding motifs, however these form intramolecular hydrogen-bonds in preference to intermolecular binding with complementary acceptor-acceptor-donor (AAD) partners. We recently reported a modification of the ureidopyridine motif, whereby the 6-membered pyridine ring was substituted for a 5-membered imidazole heterocycle, yielding a conformer independent DDA motif.[3]

Herein, we present a second hydrogen-bonding motif based on ureidopyrimidine. We reasoned that exchange of the pyridine of the ureidopyridine motif for a pyrimidine would furnish a motif with a conformer independent ADA arrangement of hydrogen-bonding sites.[4] The introduction of a second nitrogen atom into the heteroaromatic ring affords a highly preorganised unit through intramolecular hydrogen-bonding and in doing so results in a conformer independent presentation of the hydrogen-bonding groups. The association constants with complementary diamidopyridine DAD arrays are comparable to thymine derivatives.[5] This motif therefore offers an interesting alternative for incorporation into supramolecularly cross-linked polymer materials.



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# Development of Purine-Based Inhibitors of Protein Kinases

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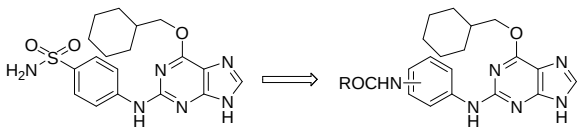
Protein Kinases constitute a family of proteins whose function is to bring about the biological activation or inactivation of a protein by catalysing phosphorylation at specific sites on the protein.[1] CDKs are one such protein kinase family. Several CDKs are well characterised and posses a diversity of functions; many are critical components of cell-cycle machinery, primarily focused on cell-cycle regulation and control. Their mutation may lead to aberrant cell cycle control which is observed in number of cancers.[1]

Previous work has indicated that purine-based compounds such as 2-arylamino-6-alkoxypurines are efficacious in the perturbation of protein kinase activity, most notably against CDK2.[2] The sulfonamide-based compound NU6102 was developed as a potent small-compound inhibitor of CDK2 with $IC_{50}$ = 5 nM.[2]




A triplet of hydrogen bonds between the purine and the hinge region of the kinase is often a prerequisite for ATP-competitive inhibition, and the presence of an $O^6$-cyclohexylmethyl motif may be imperative in the ribose binding domain the enzyme. By retaining the 2-arylamino-6-alkoxy-purine template, the opportunity to develop further protein kinase inhibitors was foreseen and synthetic work was undertaken. A number of modifications to the 2-arylamino functionality were made, including replacement of the sulfonamide moiety with a variety of different hydrogen-bond acceptors/donors including acetanilides.[3]
By reducing the affinity of the aforementioned compounds for CDK2, it is hoped that potent and selective inhibitors can be rationally designed for other kinase targets.

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# Towards the Total Synthesis of Phacelocarpus-2-pyrone A

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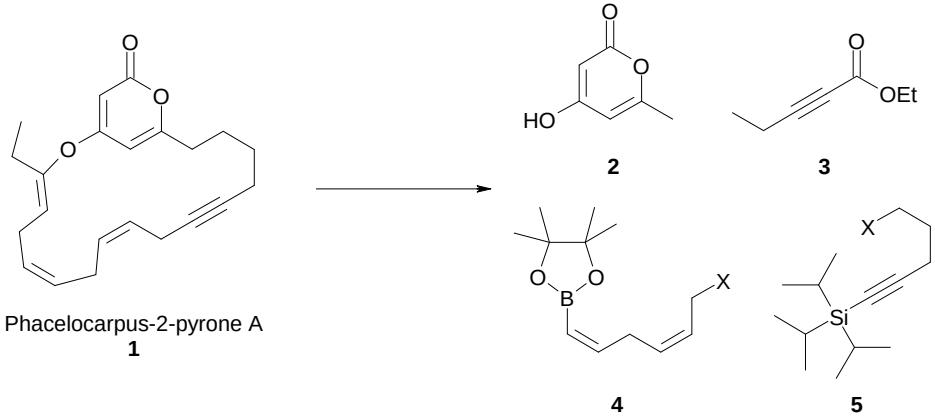
**Abstract**

The phacelocarpus pyrone natural product series comprises of approximately 12 compounds, which were first isolated in 1982 from the Australian marine red alga *phacelocarpus labilliadieri*. Each compound consists of a macrocycle containing a pyrone (either 2- or 4-type) and multiple centres of unsaturation, most notably the 1*Z*,4*Z*-skipped diene motif seen throughout the series. Biological evaluation of **1** has revealed high levels of *phospholipase A2* inhibition, and potent feeding inhibition of herbivorous shells. Crude extracts from the alga also exhibit neuromuscular blocking activity.[1]




The first synthetic strategies employed towards the total synthesis of **1** will be presented. The assembly of both right and left hand portions of **1** will be described, starting from functionalised starting materials (*e.g.* **2**-**5**). Particular attention is given to the synthesis of a novel 2-pyrone containing vinyl ether motif, which is unique to this class of natural products. Some useful cross-coupling methodology has been developed as part of this study.[2]

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# Hide and Seek Fun is over: Development of novel diagnostic reagents for micro–organism identification

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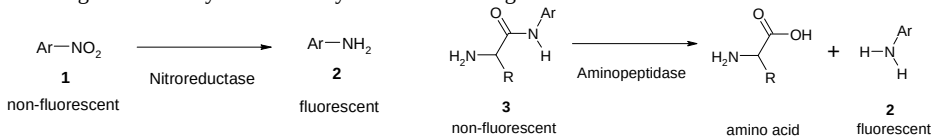
## *Background*

Amongst the several techniques of micro-organism detection, the Petri dish culture is one of easiest, quickest and most efficient that is currently used in laboratories. Depending on the culture media, the micro-organisms colonies can appear coloured[2] or fluorescent[3]. We are currently working on fluorogenic diagnostic reagents targeting bacteria which have the following enzymes in their metabolic collection: nitroreductase and aminopeptidase.

## *Detection of enzymatic activity*

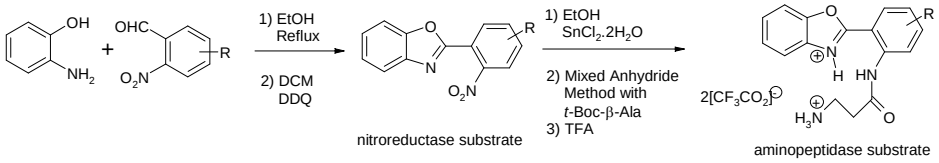
The chemicals responsible for the fluorescence must not be fluorescent when introduced in the culture media but they have to become fluorescent if there is any bacterium in the sample assessed. Things happen slightly differently for the nitroreductase[4] and aminopeptidase[5] enzymes, nonetheless the principle applied to these two enzymes remains identical: they will cleave or modify a specific part of the substrates **1** and **3** in order to reveal a fluorescent version **2** of these compounds, hence the microorganism activity is detected by the fluorescence generated.




**Nitroreductase activity** **Aminopeptidase activity**

## *Synthesis of the substrates*

The organic chemistry involved in this project is based on the synthesis of heterocyclic nitro and amide compounds as illustrated below. In addition to the benzoxazoles shown below, a series of benzothiazoles and benzimidazoles substrates have also been prepared.

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# Radical Approaches to *Alangium* and *Mitragyna* Alkaloids

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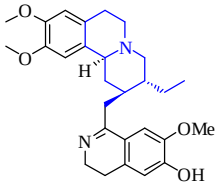
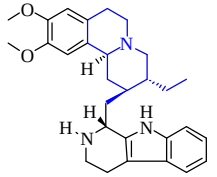
## Abstract

### 1. Introduction

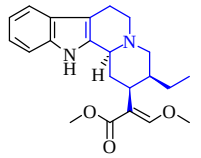
A range of *Alangium* and *Mitragyna* alkaloids possess an octahydroquinolizine ring system, including psychotrine, deoxytubulosine and mitragynine, all of which exhibit biological activity. It is proposed that a synthetic approach to the octahydroquinolizine ring system using a radical cyclisation in the key step will allow for a quick and efficient route to these alkaloids.



**Psychotrine**
Potent inhibitor of HIV-1 reverse transcriptase



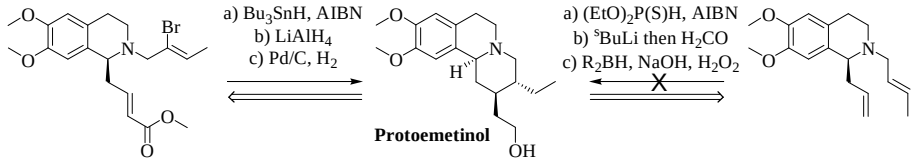
**Deoxytubulosine**
Cytotoxic and an inhibitor of thymidylate synthase



**Mitragynine**
Potent analgesic activity, principally against opioid receptors

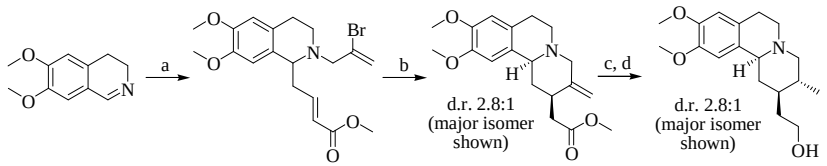
### 2. Synthetic Approaches

It is known that various *Alangium* alkaloids including psychotrine[1] and deoxytubulosine[2] can be accessed from protoemetinol. Our initial synthetic approach to protoemetinol investigated a thiophosphite based radical addition/cyclisation reaction of a 1,7-diene, but this route proved unsuccessful. Subsequent investigations explored the 6-*exo* radical cyclisation reaction of a vinyl bromide, followed by reduction of the ester and hydrogenation of the alkene.




### 3. Model Studies

Model studies were directed towards the synthesis of a demethyl version of protoemetinol. The desired vinyl bromide was prepared by a one-pot procedure combining *N*-allylation with an organozinc addition to a C=N bond. Reaction of the vinyl bromide with $Bu_3SnH$ and AIBN, results in the desired tricycle, which can be reduced to give (±)-demethyl-protoemetinol in an overall yield of 49% over 4 steps.




a) 2,3-Dibromoprop-1-ene, $Et_2O$, rt, 24 h then (*E*)-methyl 4-bromobut-2-enoate, Zn, MeCN, rt, 36 h, 79%; b) $Bu_3SnH$, AIBN, THF, reflux, 6 h, 78%; c) $LiAlH_4$, THF, 0 °C to rt, 6 h, 87%; d) 5% Pd/C, $H_2$, MeOH, 91%.

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# Direct-Arylation of Purine Nucleosides

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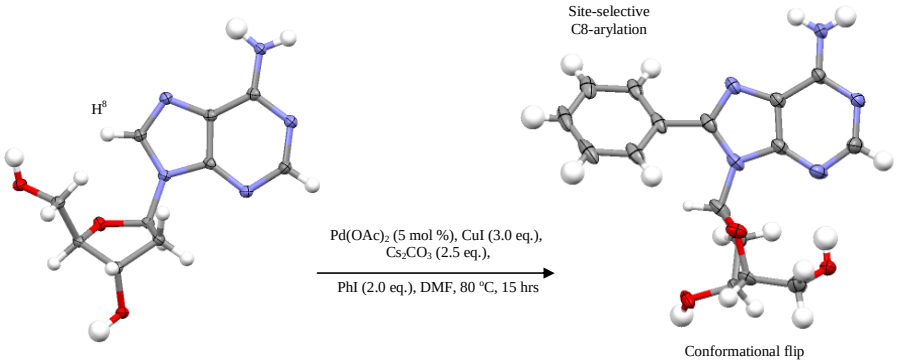
**Abstract**

8-Modified purine nucleosides are widely used as pharmaceutical agents and biochemical probes.[1] The development of simple synthetic routes to this class of compounds by exploiting transition metal catalysis would be advantageous for the above applications. The development of a new, efficient palladium- and copper-mediated direct-arylation methodology has been achieved, enabling the formation of 8-aryl adenosines in one step from adenosine. This methodology has also been applied in the synthesis of the less stable 8-aryl 2'-deoxyadenosines. Optimisation of the reaction had to be performed to accommodate the lower stability of the β-glycosyl in order to prevent degradation *via* deglycosylation. A range of aromatic groups can be effectively coupled, including heteroaromatic and polar substituted aryl halides. A library of adenosine and 2'-deoxyanalogues were synthesised without the need for sugar or base protecting groups.[2] The products were found to adopt a *syn* C2'-*endo* conformation.




The substrate scope was explored with the arylation of a number of naturally occurring and synthetic purine nucleosides. Both purine and sugar modifications are tolerated with adequate to excellent yields obtained of the arylated products, although the guanine moiety was found to inhibit/impede the reaction. An in-depth study into factors which affect the reaction was performed, palladium source, catalyst loading, the nature of the active catalytic species, source of C8 selectivity and the role of the copper were all examined. This methodology facilitates the rapid production of modified nucleosides, and provides further insight into the mechanism of direct-arylation reactions.

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# Novel Synthesis of 3-Aminooxindoles: The Road to Psychotrimine

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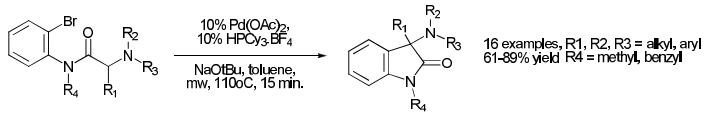
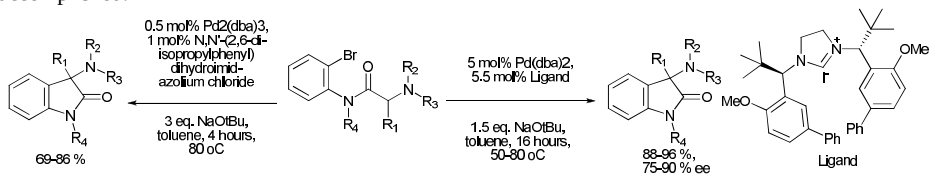
**Introduction**: 3-Aminooxindoles are present in many biologically active compounds. Despite this fact there are limited methods for their synthesis and no examples to date of asymmetric routes. We outline the key events in the development of a novel route to the 3-aminooxidole structure, including an asymmetric variant, and also highlight our efforts to showcase this methodology in a total synthesis of psychotrimine.

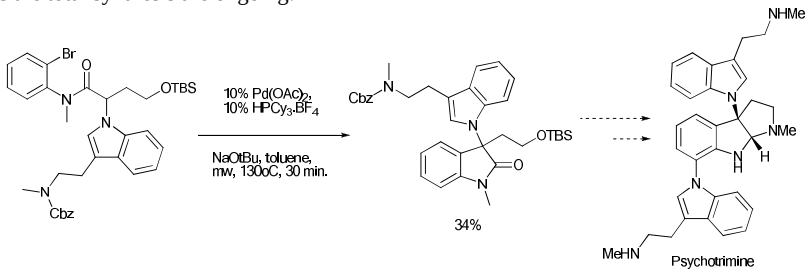
**Discussion**: We proposed the intramolecular α-arylation of amide enolates as a possible asymmetric route to 3-aminooxindoles. Substrates for the key reaction were synthesised in 3 steps from readily available starting materials, in good to excellent yield. Initially the commonly used arylation conditions of Hartwig[1] were utilised but gave very poor conversion; after some development the following optimal conditions were identified.




Using these conditions a variety of substrates with different steric and electronic properties were successfully arylated in good yield.[2] The initial conditions were perfect for the high throughput screening of substrates on small scale, but the use of microwave heating and relatively high catalyst loadings restricts the use of these reactions on scale. We therefore further optimised the reaction, finding that the application of *N*-heterocyclic carbene ligands allowed for a significant reduction in both reaction temperature and catalyst loading. The 1 mol% loading of Pd is lowest recorded for an amide enolate arylation reaction. By screening different NHC ligands, Pd sources and solvents the reaction conditions below were established. In collaboration with the Kündig group, asymmetric versions of this reaction have been investigated and thus far up to 90 % *ee* (with >90 % yield) has been accomplished.[3]




A synthesis of the natural product psychotrimine was proposed via a 3-aminooxindole intermediate. This intermediate has been successfully synthesised using the developed methodology, and efforts towards the total synthesis are ongoing.




**References**

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# Synthesising the Novel Antibiotic Thiomarinol A

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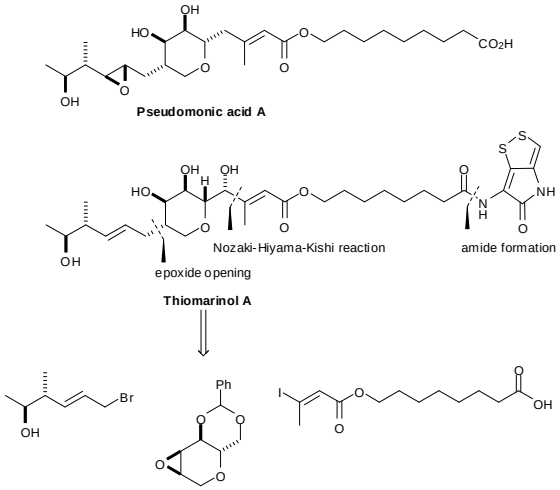
**Abstract**

Thiomarinol A is an antibiotic isolated from *Alteromonas rava* sp. nov. SANK 73390, a marine bacterium found on the sponge *Darwinella rosacea*[1]. It is structurally related to the pseudomonic acid[2] antibiotics, one of which, pseudomonic acid A, is used to prevent colonisation of MRSA bacteria in the nasal cavity[3] and as a topical cream to treat bacterial skin infections under the name Bactroban®. Unfortunately pseudomonic acid A has poor bioavailability and loses efficacy outside the pH range 4-8[4] making the search for an alternative appealing. This has drawn attention to thiomarinol A which has shown impressive antibacterial activity[1], against a wider range of bacterial strains than pseudomonic acid A.




The proposed highly convergent synthesis of thiomarinol A relies on two key C-C bond forming reactions. Firstly the opening of an epoxide derived from D-(+)-xylose then a Nozaki–Hiyama–Kishi reaction to introduce the α,β unsaturated ester. A final amide formation will give rise to thiomarinol A.

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# Using glycosyl transferases for glycoside synthesis

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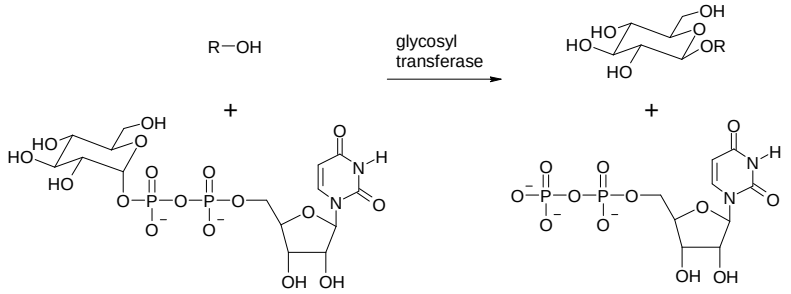
**Abstract**

One methodology which can be used to increase the solubility of organic compounds in aqueous media, and indeed *in vivo* is to couple the molecules to a carbohydrate moiety, a strategy commonly exhibited by phase II metabolism. Chemical methods of coupling of a carbohydrate to such a molecule often require low yielding reaction conditions and time consuming protecting group regimes. Mimicking Nature's enzymatic processes to perform this addition is an obvious source of inspiration for an alternative, biocatalytic, process. Much work has been done on using glycosidase enzymes to effect glycosyltransfer reactions wherein control of reaction conditions provides an alternative nucleophile to water can be used to build carbohydrate conjugates through either reverse hydrolysis or transglycosylation. An alternative biochemical pathway which is exploited is the use of glycosyl transferases (GTs) which is used *in vivo* for biosynthesis of oligosaccharides. One drawback to the use of these enzymes in chemical synthesis has been the combination of their exquisite selectivity for the substrates and the glycosidic bond to be formed, and the lack of readily available GTs.




In this project we are using molecular biology techniques to clone into *E. coli* DNA which will encode for a range of GTs we have chosen on the basis of interesting homologies in the primary sequence from the vast array of microbial genome data which is publically available. After purification, we are then testing them against a panel of donor nucleoside diphosphate sugars and acceptor alcohols. We then hope to use the best yielding conversions as the basis for optimization by forced evolution. We will report early results which have shown significant activity in our initial panel of enzymes in the addition of both glucose and galactose to both alkyl and aryl alcohols.

## Discovery of novel BACE1 inhibitor scaffold using *in silico* high throughput screening

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[b] Institute of Molecular and Cellular Biology, and Leeds Institute of Genetics, Health and Therapeutics, University of Leeds, Leeds LS2 9JT, UK

**Background:**
Beta-secretase (BACE1) is the first enzyme involved in the amyloid cascade hypothesis which cleaves the amyloid precursor protein (APP) into amyloid beta-peptide. Since the accumulation of amyloid beta-peptide into insoluble plaques is one of the key events in the pathogenesis of Alzheimer's Disease, BACE1 is considered an attractive therapeutic target for the development of small molecule inhibitors. Virtual high throughput screening is becoming an integral part of the drug discovery process due to its relatively low cost compared to conventional high throughput screening strategies. The recent availability of new X-ray crystallographic structures of BACE1 enzyme-inhibitor complexes has facilitated the discovery of small molecule inhibitors using molecular modelling methods.

**Methods:**
*In silico* screening of three commercially available libraries containing a total of 300,000 compounds against BACE1 was undertaken using the docking algorithm eHiTS, and the 100 highest-scoring compounds from each library prioritised. Compounds were triaged based upon their predicted binding affinity and physicochemical characteristics. Six compounds were tested in an *in vitro* enzyme activity assay using a quenched fluorescent peptide substrate based on the Swedish mutant APP sequence (SEVNLDAEFK).

**Results:**
Based on an isatin motif, compound **5** was found to have an $IC_{50}$ of 2.4 μM towards BACE1. Structural analogues of the hit compound were synthesised to probe the structure-activity relationships (SAR) of the inhibitory effect. The SAR studies revealed the important features of the inhibitor, including a *p*-nitrophenol and a *p*-tolylamide scaffold. Further *in silico* docking studies suggested compound **5** may bind within the BACE1 active site through H-bonding interactions between the *p*-tolylamide and the catalytic aspartate residue Asp228.

**Conclusions:**
The combination of an *in silico* approach with validation by *in vitro* enzyme assays have led to the discovery of a new BACE1 inhibitor scaffold.

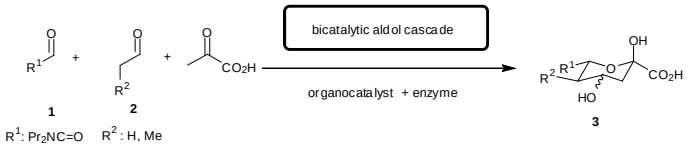


## Combined organocatalytic / enzyme-catalysed cascades: Exploitation in natural product-like molecules

***Angela Kinnell***, [a] Prof.. Adam Nelson, * Dr Alan Berry, * and Dr Matilda Bingham [b], The School of Chemistry, University of Leeds [a,] Organon [b]; chmadk@leeds.ac.uk, 0113 3436436

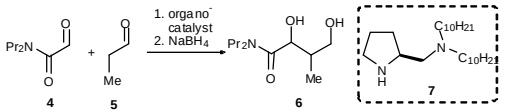
**Three-component reactions are synthetically powerful but relatively rare in organic chemistry.**

**Three component one-pot reaction strategy:** The combination of organocatalysis with enzymes is as yet unreported. We have developed the first one-pot reaction which combines organocatalysis with enzyme catalysis in a three-component reaction. The bicatalytic tandem aldol cascade uses aqueous organocatalysis and an evolved pyruvate aldolase (uniquely available to us, and highly diastereoselective) to guide the assembly of small molecule building blocks such as **3.** This approach reduces the current syntheses of these sialic acid derivatives from nine steps to one.

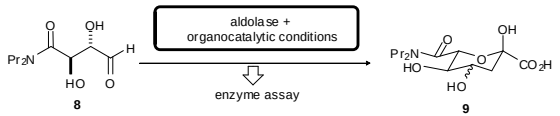



**Development of a one-pot reaction – the three stages: A)** Establishment of organocataysed conditions in buffer; **B)** identification of conditions under which BOTH enzyme catalysis and organocatalysis can occur, using an enzyme assay and **C)** combination.

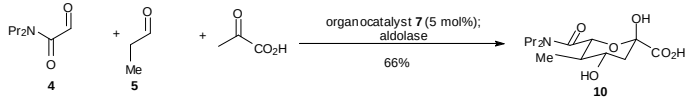
**Stage A):** Screening a number of prepared organocatalysts with initial substrates **4** and **5** revealed that diol **6** could be prepared in moderate yield in a range of solvents. The best yields and diastereoselectivities were obtained with catalyst **7** which was suitable for use in buffer.




**Stage B):** The ability of the aldolase to catalyse the aldol reaction of aldehyde **8** was investigated under the organocatalytic conditions, in order to determine their compatibility. This was achieved using an enzyme assay.




**Stage C):** The unprecedented combination of organocatalysis with enzyme catalysis in a one-pot three component reaction has been successfully achieved. The aldehyde **4** underwent two sequential aldol reactions with aldehyde **5** and pyruvate to give the acid **10** in good yield (66%).




Defining the reaction's scope and limitations by variation of substrates is the next major goal of the project. The chemistry developed will be applied to the synthesis of highly functionalised lactone building blocks for natural product synthesis, for example Prelactone B or natural product-like molecules.

# The Application of Novel Oxathiane Glycosyl Donors in the Stereoselective Synthesis of 1,2-*cis* Glycosides

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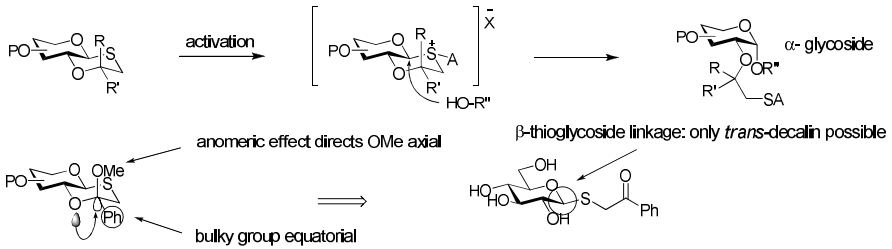
**Abstract**
The major challenge in oligosaccharide synthesis is the stereoselective formation of 1,2-*cis* glycosides. Despite significant advances, modern synthetic carbohydrate chemistry has still yet to provide a general method for the efficient synthesis of 1,2-*cis* glycosidic linkages. Recent work by Boons and co-workers [1] utilised a chiral auxiliary based approach to the problem. 1,2-*cis* Glycosides were synthesised in good yield with excellent selectivity via a trans decalin intermediate.

We have developed novel oxathiane glycosyl donors **1** that mimic this *trans*-decalin intermediate and act as *stereoselective* glycosyl donors, the first example of which is the oxathiane ketal **2**. Advantages include; a concomitant glycosyl donor/ chiral auxiliary strategy with little need for extensive protecting group strategies, expedient synthesis of the oxathiane scaffold, and stereoselective oxathiane ring formation exploiting the anomeric effect.




**References**
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# SYNTHESIS OF NOVEL RETINOID ANALOGUES FOR CONTROLLING SELECTIVE STEM CELL DIFFERENTIATION

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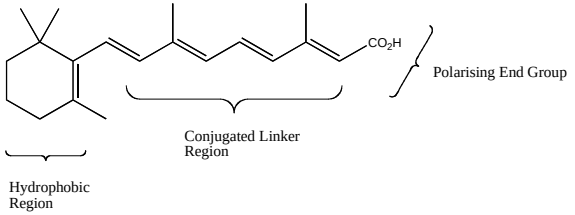
The retinoids are a group of greater than 4000 natural and synthetic molecules that are structurally and/or functionally analogous to Vitamin A. All-*trans*-retinoic acid (ATRA) is the major metabolite of vitamin A and has essential roles in cellular proliferation, differentiation and morphogenesis as well as embryonic development and apoptosis.[1] ATRA and its two naturally occurring isomers, 9-*cis*-retinoic acid (9CRA) and 13-*cis*-retinoic acid (13CRA) have also been identified as the natural ligands for the retinoid superfamily of nuclear receptors (retinoic acid receptors, RARs and the retinoic X receptors, RXRs), and thus function as powerful transcription factors.[2] However, due to the extended polyene chain, these molecules are particularly susceptible to photoisomerisation, leading to a mixture of retinoic acid isomers and degradation when used for *in vitro* studies.

ATRA




Our work is aimed at the synthesis of a set of novel synthetic retinoid compounds. All still contain the three major characteristic binding regions (shown above), but are less likely to undergo isomerisation and/or oxidation, and are therefore easier to handle and have greater selectivity. The synthesis of such compounds has been achieved through a number of palladium-catalysed coupling reactions, including both Sonogashira and Heck-Mizoroki couplings. In addition, a key stereoselective iododeboronation reaction is employed to control alkenyliodide geometry, achieving either inversion or retention of the stereochemistry, and hence, enabling the formation of both *cis*- and *trans*-product isomers.[3] Introduction of both an aromatic ring and an alkyne functional group has aided in the stabilisation of product compounds, while retaining a conjugated linker region. The compounds produced have subsequently been biologically assessed using two model systems, a human embryonal carcinoma stem cell line, TERA2.cl.SP12, which represent a pluripotent stem cell model of early embryogenesis,[4] and a mouse F9 murine EC cell line containing a stable LacZ reporter line for the retinoic acid response element.[5]

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# $CO_2$ / Amine adducts in Novel Purification Techniques

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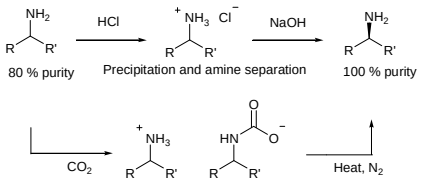
**Abstract**

The clean-up and disposal of industrial waste streams increases the cost and number of steps of any chemical process. Typical amine purification methods, for example, involve precipitating the hydrochloride salt form of the amine, followed by neutralisation to regenerate the free amine thus producing large volumes of aqueous waste which require costly treatments. We propose to reduce this cost by simplifying the purification process *via* the formation of crystalline ammonium carbamate salts. After reaction of amines with carbon dioxide ($CO_2$), the crystalline carbamates can be filtered from the crude reaction mixture and the free amine regenerated upon heating. Carbon dioxide is released as a gas which can be recycled within the process, eliminating the production of aqueous waste (Scheme 1).




**Scheme 1**

Initial investigations have given some insight into the nature of carboxylation and decarboxylation of a range of low molecular weight primary and secondary amines (Figure 1). Variable carboxylation rates were observed to yield either a colourless solid or viscous oil. In general, the least hindered amine (*e.g.* **1 – 3** and **5**) will react faster than a more hindered amine (*e.g.* **4**). The decarboxylation was also investigated using differential scanning calorimetry (DSC) and thermal gravimetric analysis (TGA). In general, secondary amines (**4** and **5)** decarboxylated at lower temperatures (~ 45 – 50 °C) than primary amines (**1-2;** up to 140 °C). This suggests that effects such as steric hindrance around the nitrogen, pKa or other potenetial hydrogen bonding sites will influence the ease at which $CO_2$ will interact with an amine.

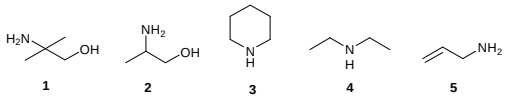



**Figure 1:** Examples of amines examined

If the original amine mixture exists in an enantiomeric excess, then the carbamate salts formed will be diastereomeric (Figure 2). Due to differing solubilities, one diastereomeric salt will precipitate preferentially to the other allowing diastereomeric separation. We have been successful in increasing the optical purify of α-methylbenzylamine from 80 % *ee* up to as much as 98 % *ee* using this approach.

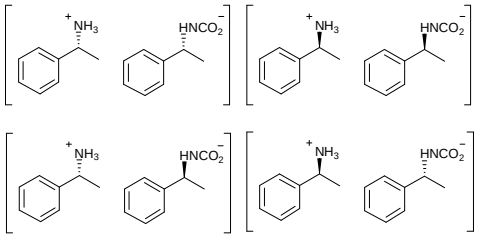


**Figure 2:** Possible diastereomeric salts



# Toward Protein Surface Recognition Using Metal Complexes

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The challenge of developing a system to modulate protein function through surface recognition is a daunting task. Prospective molecules must cover a large area (~1200 Å$^2$) of a relatively featureless protein surface, where non-contiguous interactions occur over a large surface area.[1,2]

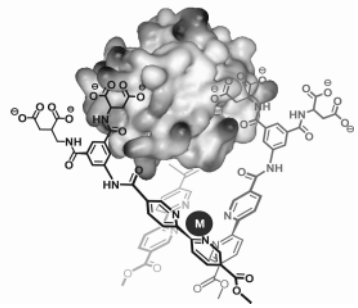


**Fig. 1**: Representation of how or metal complexes bind and recognise a protein surface

Our work focuses on the synthesis of functionalised bipyridine metal complexes that project binding functionality over a large surface area[3] (Fig. 1). Coordination complexes are attractive because of the diverse geometrical presentation of functional groups that can arise as a consequence of the stereogenic metal centre and the ability to assemble the complexes under kinetic or thermodynamic control.

In this presentation we will illustrate our strategy and present preliminary synthesis and screening results. Successful implementation of a protein assay has allowed us to show that very simple bipyridine complexes[4] bind to the exposed heme face of cytochrome *c*.

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**P27**

# The Development of Pyrimidine-based ATP Competitive Inhibitors of Protein Kinases

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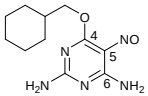
**Abstract**

Protein kinases are of immense significance in the context of controlled cellular development and progression. Aberrant activity of protein kinases is known to be a key pathway *via* which cancer develops. Modulation of kinase activity *via* the administration of selective ATP competitive inhibitors is a proven chemotherapeutic approach.

Previous work within the Northern Institute for Cancer Research has focussed upon the development of pyrimidine-based ATP competitive inhibitors of cyclin-dependent kinase 2 (CDK2)[1]. Further development is aimed at the diversification of the pyrimidine scaffold with a view to hit determination against alternative protein kinases, whilst abolishing CDK2 activity.

The 5-nitrosopyimidine derivative NU6027 was taken as an initial starting point for synthetic work appertaining to the elimination of CDK2 activity. Synthetic studies have been focussed upon the production of small libraries of compounds with systematic modification of the 4-, 5- and 6-positions of the pyrimidine scaffold. Techniques utilised include a microwave assisted multiple parallel approach for efficient synthesis of target compounds.



**NU6027**
CDK2 $IC_{50}$ 2.2 µM

A key structural feature of NU6027 is the presence of an intramolecular hydrogen bond between the nitroso group and an adjacent amino NH. The relevance of this for biological activity is being explored by making judicious modifications to these groups. The cyclohexylmethyl group of NU6027 is known to occupy the ribose binding pocket in CDK2. Abolition of this interaction is being explored by selective modifications within the cyclohexyl ring.

**References**

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**P28**

# Look, no *ortho* substituents! Slow rotation about a single bond between $sp^2$- and $sp^3$-hybridised carbon atoms

**Sarah Murrison**, Ben McKeever-Abbas, Adam Nelson* and Stuart Warriner *

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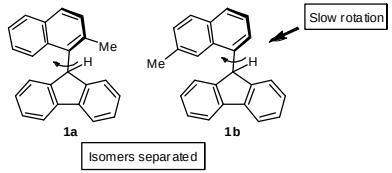
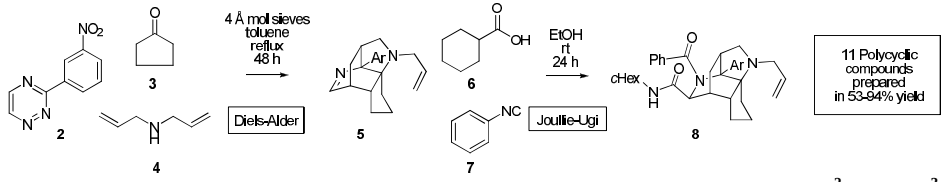
## 1. Precent for slow rotation

There are no examples in the literature where isomers, due to restricted rotation, have been separated without *ortho* substituents.



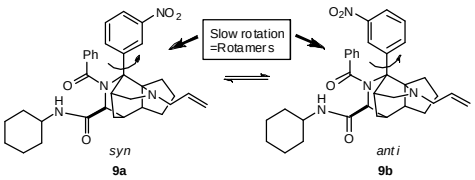

**The Diels–Alder cascade and Joullié–Ugi reaction**

The Diels–Alder cascade generates a polycyclic imine with excellent stereocontrol. The cascade involves the generation of an electron rich enamine (from **3** and **4**), which undergoes an inverse electron demand Diels–Alder reaction with the electron deficient triazine **2**. A retro-Diels–Alder reaction, followed by an intramolecular Diels–Alder, affords the polycyclic imine **5**. We have further diversified the polycyclic imine by exploiting a 3 component Joullié–Ugi reaction.




**Physical organic approach to the slow rotation about a single bond between $sp^2$- and $sp^3$-hybridised carbon atoms**

Analysis of the $^1$H NMR spectrum led to an interesting and unprecedented observation when the polycyclic structure **9** contained a *meta*-substituted nitro group (Ar). Limited rotation between the bridge end carbon and the aryl group gave rise to rotameric isomers. To our knowledge, this is the first example of slow rotation (between $sp^2$- and $sp^3$- hybridised carbons) in a molecule lacking an *ortho* substituent.




We have investigated the kinetics of the slow rotation using variable temperature NMR or variable temperature HPLC, according to the timescale of the rotation. We have also investigated the structure activity relationship (SAR) of the slow rotation and the results are summarised below.

# Gd-loaded Gold Nanoparticles as Contrast Agents for MRI

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**Abstract**

Magnetic resonance imaging (MRI) is a powerful diagnostic technique used in modern biomedical research. MRI is based on nuclear magnetic resonance (NMR). It has many advantages over other techniques as it is non-invasive and has excellent spatial resolution. The use of contrast agents (CAs) further enhanced its success by changing the signal intensities. The contrast agents (CAs), mostly gadolinium based, affect the intensities of proton NMR signals by altering the relaxation rate of water protons in the body [1]. The maximum relaxivity can be achieved by slowing down the tumbling of contrast agent molecules and attaching several gadolinium ions per molecule. To get maximum relaxivity, gold nanoparticles (AuNPs) [2] stabilized by new DTPA (diethylenetriaminepentaacetic acid) based ligand were prepared and then gadolinium ions were loaded [3]. The spin lattice relaxivity (R1) of Gd-loaded-AuNPs was measured and compared with commercially available MRI contrast agent i.e. Gd-DTPA. Gd-loaded-AuNPs showed 27% more Ra than Gd-DTA. Further increase (i.e.71%) in R1 was found by formation of Polyethyleneimine (PEI) layers around AuNPs. A recognition vector (biotin terminated thiol) was synthesized and then attached on Gd-loaded-AuNPs and they were found to successfully recognize their target [4].

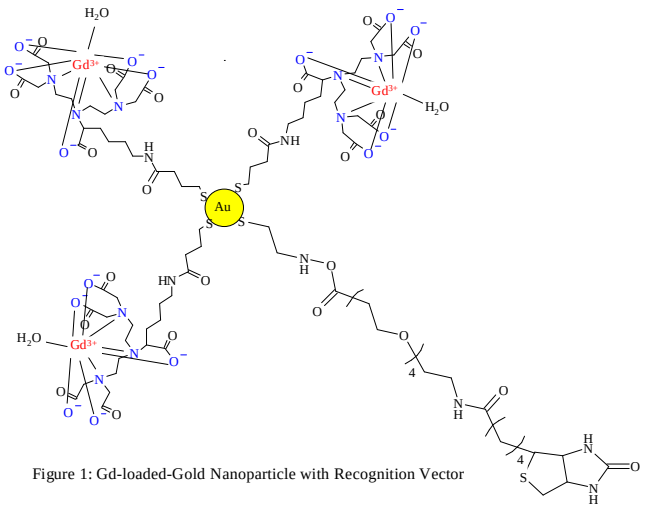


Figure 1: Gd-loaded-Gold Nanoparticle with Recognition Vector

## References

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# Towards the Synthesis of Stable Analogues of Viridenomycin

***V.E.O'Connor*** *and A.Whiting**

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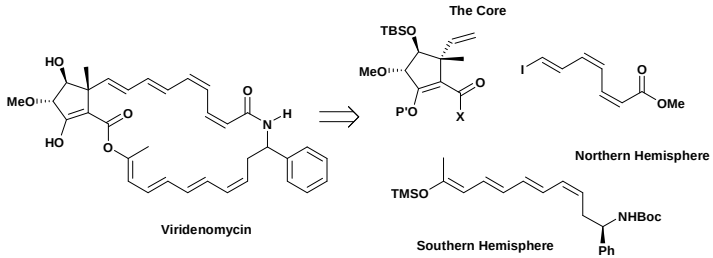
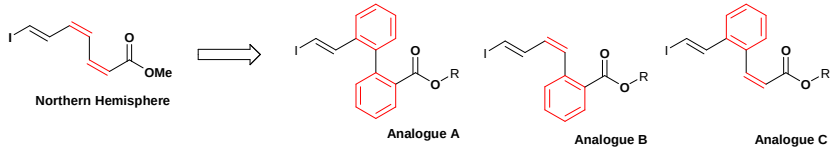
**Abstract**

Viridenomycin is a largely polyene containing natural product which has been shown to have potentially significant anti-leukaemic activity. It is structurally complex, and thus provides a challenging target for total synthesis, which has so far remained elusive. The basic retrosynthetic plan is shown below.




Previous efforts in its total synthesis have shown the *cis-cis* diene portion of the northern hemisphere fragment in this molecule to be particularly unstable,[1] suggesting that more stable analogues may be of significant use. In order to stabilise the molecule, a *cis* locking component has been designed into the structure of the northern hemisphere, in the form of either a single or two benzene rings. This has given a total of 3 plausible analogues worth synthesising (A-C).




The exploitation of Suzuki-Miyaura and Heck-Mizoroki cross-coupling methodology in achieving this has been dominant and effective. The SM methodology required considerable modification but has been applied successfully in the synthesis of the northern hemisphere of analogue A, which is currently close to completion. The HM coupling methodology in conjunction with some sophisticated iodo-deboronation methodology[2] has produced analogue B. An efficient amide coupling has also been developed, which we hope can be applied in the coupling of the northern and southern hemisphere fragments, applying it in addition to the total synthesis of viridenomycin itself. It is also envisioned that the HM conditions developed can be applied in the coupling of these fragments to the core, models have which have been tested.

Synthesis of analogue C has proved problematic, and a small degree of experimentation with Sonogashira and Negishi type alkynyl coupling has thus far proved fruitless, however, we remain steadfast in this synthetic route, as room for variation remains vast.

## References

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# Dissecting the Function of Glutamate Transporters: A Chemical Genetics Approach

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## Abstract

L-Glutamate (Glu) is a key signalling molecule in the mammalian central nervous system. Glu's pathway is an integral part of the majority of normal brain functions, including cognition, learning and memory. Seven amino acid transporters have been identified in the human genome that catalyses the removal of Glu from the synapse preventing neurotoxicity. Attempts to dissect their individual roles through reverse chemical genetics have been hampered by the lack of potent and selective inhibitors for each isoform. Diversity oriented synthesis has inspired the production Glu transporter targeting building blocks which can be coupled to other building blocks followed by skeletal transformation via ring closing enyne metathesis to produce a skeletally diverse library of compounds (Figure 1). The library can then be screened against each isoform which are over expressed in HEK293 cells in a simple fluorescence based assay to identify potent and selective ligands. Analogues of potent ligands can then be synthesised via combinatorial chemistry allowing the chemical space of each isoform to be rapidly explored. The effects of isoform-selective inhibitors on glutamatergic transmission will be tested using electrophysiological approaches to help elucidate the physiological functions of individual excitatory amino acid transporters at system levels.

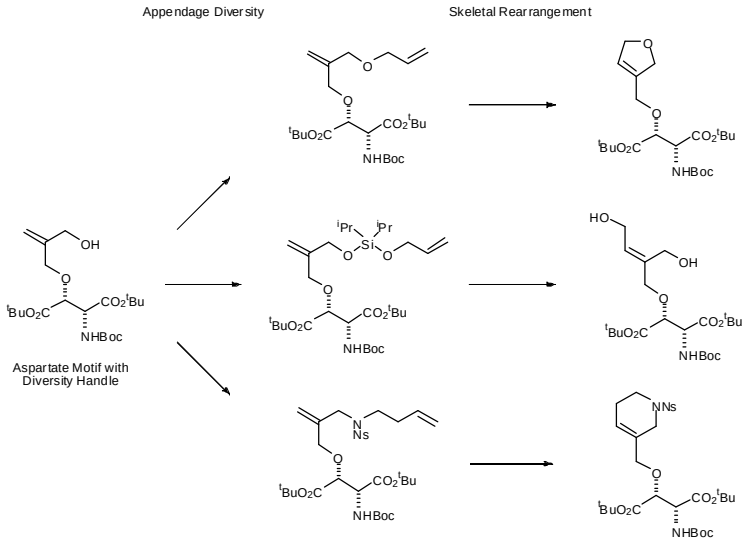


**Figure 1**: Diversity oriented synthesis of glutamate transporter ligands



# Design, Synthesis and Biological Evaluation of Novel Dihydroorotate Dehydrogenase Inhibitors

Deborah Cowen University of Leeds Colin W. G. Fishwick and A. Peter Johnson

## Abstract

Malaria is thought to affect >40 % of the world's population causing 1 – 3 million deaths per year. Malaria is caused by *Plasmodium* parasites, of which there are four species and most fatal cases of malaria are caused by *Plasmodium falciparum* which is transmitted to humans *via* the female anopheline mosquito. Resistance to almost all currently used antimalarial treatments for *P. falciparum* infection is a growing problem, therefore new treatments or combinations of known treatments with therapy related to novel targets is of great interest.[1] Dihydroorotate dehydrogenase (DHODH), an essential enzyme within this pathogen, catalyses the rate limiting fourth step of the *de novo* pyrimidine biosynthetic pathway[2], which is essential for nucleic acid synthesis. The parasite is completely dependent on this method of pyrimidine biosynthesis and, unlike humans, cannot make use of the alternative salvage pathway which recycles pyrimidines from other sources. While an inhibitor which is selective for PfDHODH versus HsDHODH is desirable, even non selective inhibition of *Pf* DHODH could provide a useful therapy.

Over the past few years we have carried out an extensive search for good inhibitors of *Pf*DHODH. This has included extensive biochemical studies to characterise the enzyme, protein crystallography of several co-crystallized enzyme/inhibitor complexes and chemical studies to design and synthesize potential inhibitors. Tools for structure based design have included the shape similarity program, ROCS, applied to an existing inhibitor as a method of identifying commercially available compounds which may be able to inhibit the target enzyme. The result of this screening identified a potent and selective *Pf*DHODH inhibitor.

Application of the *de novo* molecular design program SPROUT[3], developed at Leeds, gave rise to a new class of inhibitors, members of which show selectivity for either *Plasmodium* or human DHODH and a picture is emerging as to the molecular requirements for potent and selective DHODH binding. (*Figure 3*)

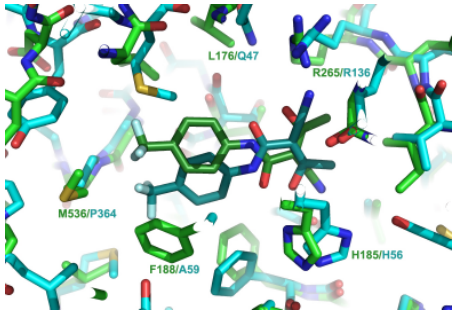


***Figure 3.*** *Known inhibitor A77 1726 bound to PfDHODH (green) and HsDHODH (blue)*

## References

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# $\mu_2$-Alkyne Dicobalt(0)hexacarbonyl Carbon Monoxide Releasing Molecules

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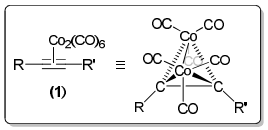
**Abstract**

Carbon monoxide has been identified as an important biological molecule that is produced within the body by the catabolism of haem.[1] It has been found that this production is up-regulated under certain stressful conditions, for example haemolytic disease, asthma, cystic fibrosis and diabetes. This interesting observation has led to the administration of CO to prompt beneficial responses. The therapeutic properties that have been discovered include: activity against systematic and pulmonary hypertension, intestinal disease, hemorrhagic shock and lung injury, it has also proved beneficial in cardiac, renal and small bowl transplants, CO also has anti-inflammatory.

Two different technological solutions to deliver CO to the body have emerged. The first is the administration of gaseous CO to the patient. The second, more elegant solution, uses carbon monoxide-releasing molecules (CO-RMs), it is this approach that this research follows. The CO-RMs chosen for study are $\mu_2$-alkyne dicobalt(0)hexacarbonyl complexes(**1**), the rationale is that under synthetic conditions one of the carbonyl ligands dissociates to allow complexation of an alkene, this is a key step in the Pauson-Khand reaction that results in the formation of cyclopenteneones.[2] It was proposed that the lability of these COs in synthetic conditions could be paralleled in physiological conditions. It is also postulated that changing the substituents on ligand will allow the release rate to be tuned. Also of significance is that several examples of this type of complex have shown biological activity.[3]




| | R | R' |
|---|---|---|
| **1a** | $CO_2Me$ | H |
| **1b** | $CO_2Me$ | $CO_2Me$ |
| **1c** | $CH_2OH$ | H |
| **1d** | *t*-Bu | H |
| **1e** | Ph | H |
| **1f** | Ph | Ph |

**Figure 1.** $\mu_2$-Alkyne dicobalt(0)hexacarbonyl complexes

We report the successful identification of a new class of CO-RM which released CO, measured by monitoring the conversion of deoxy-myoglobin to carbonmonoxy myoglobin in physiological conditions *in vitro by* UV-vis spectroscopy. The nature of the substituent was found to be critical in controlling the CO-release rate of these molecules. Further testing was undertaken and the toxicity of these complexes was established. The anti-inflammatory activity of these CO-RMs was probed by testing their ability to inhibit the production of NO in stimulated cells, some of the prepared complexes were found to elicit encouraging therapeutic responses. Interestingly, complexes that had not displayed any CO-release in the myoglobin assay showed surprising anti-inflammatory behaviour.

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# Fragment based design of cholera toxin inhibitors

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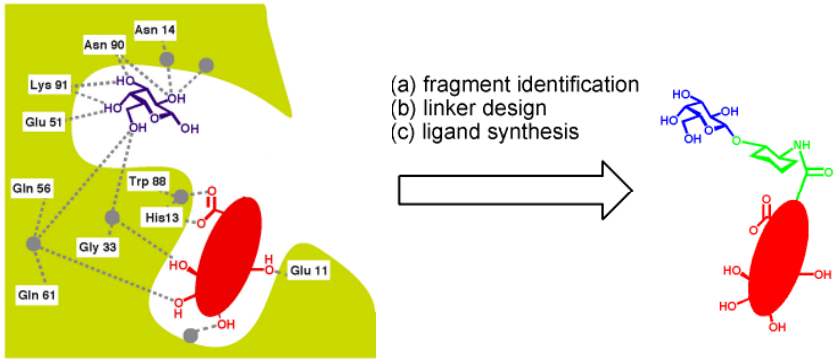
**Abstract**

Cholera is a potentially fatal bacterial disease; without treatment, death can occur within hours of infection. Cholera toxin is an $AB_5$ protein with five identical B-subunits which are responsible for binding to the ganglioside GM1 pentasaccharide on the surface of cells that line the gut. Perturbing this binding interaction would nullify the toxicity of the protein.

In this poster we will describe a fragment-based approach to designing inhibitors of cholera toxin. Binding studies of GM1 have shown that a terminal galactose residue contributes a large portion of the binding energy.[1] Therefore, this galactose residue will be included in the final inhibitor. High throughout virtual screening of fragment compounds has been used to identify fragments which might bind to the protein simultaneously alongside the galactose. Fragments that are found to bind in close proximity to the galactose will be linked to the sugar to create the inhibitor.

A small library of fragment compounds have been synthesised and screened using WaterLOGSY NMR spectroscopy to detect binding. X-ray crystallography and 2D-NMR techniques are being used to further elucidate the binding mode of these fragment compounds.

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## Developing natural product fragments *via* transannulation chemistry

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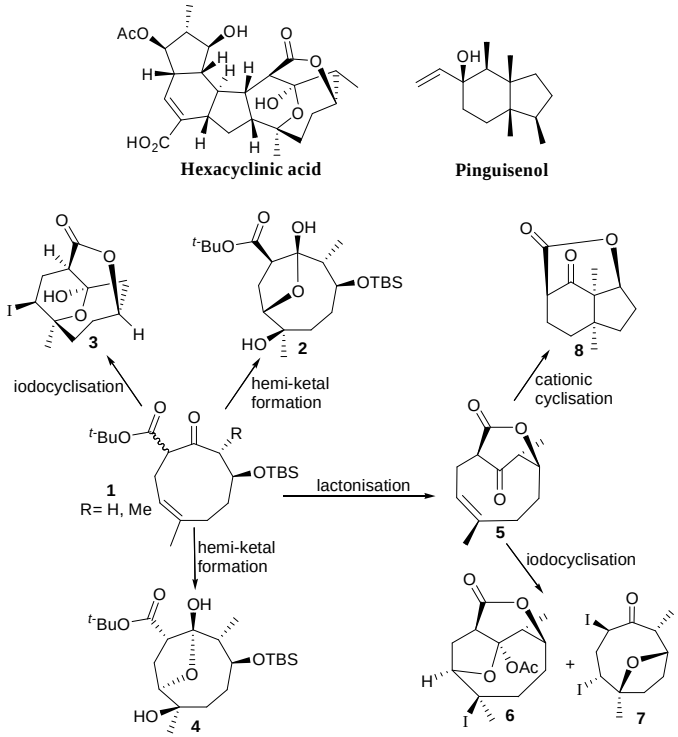
Transannulation chemistry[1] is a powerful tool for the construction of polycyclic ring systems which are present in many natural products. A summary of the transannulation reactions developed for the synthesis of natural products such as hexacyclinic acid[2,3] and pinguisenol[4] are given in **Scheme 1**, and a full discussion of the synthetic strategy will be presented in the poster.




**Scheme 1:** Summary of transannulation reactions

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## Efforts towards the total synthesis of Viridamide B

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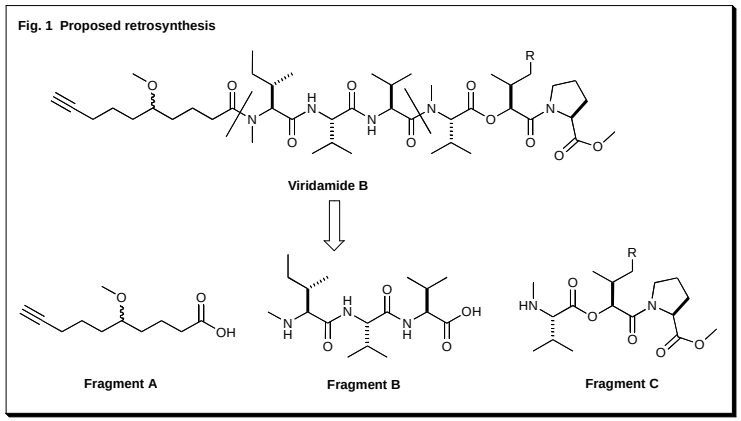
**Abstract**

*Leishmania* are protozoan parasites that can cause the neglected tropical disease leishmaniasis in humans. Upon infection this disease can inflict severe disfigurement of skin tissue and in the worst cases death. It currently affects an estimated 12 million people a year and a further 350 million people live at risk of infection. There are no effective vaccinations and drug molecules currently used are costly and on the brink of becoming obsolete as parasite resistance increases.[1] To tackle this problem we are interested in designing new peptide based anti-leishmanial agents.

Viridamide A and B were recently isolated from the marine cyanobacteria *Oscillatoria nigro-viridis* and were shown to have activity against *Leishmania* parasites in the μM range.[2] In order to investigate the potential that these compounds may have in the development of new anti-leishmanial agents we are in the process of completing the first total synthesis of both Viridamide A and B. Our retro-synthetic approach towards the synthesis of Viridamide B is shown in **Fig. 1**. Our convergent approach to Viridamide B involves the synthesis of three separate fragments and is suitable for the future preparation of different analogues of the natural product. In addition to preparing material for biological testing our total synthesis of Viridamide B will also help to determine the stereochemistry of the methyl-ether located on the fatty acid side chain of the molecule.

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# Isoindolinone-based inhibitors of the MDM2-p53 protein-protein interaction

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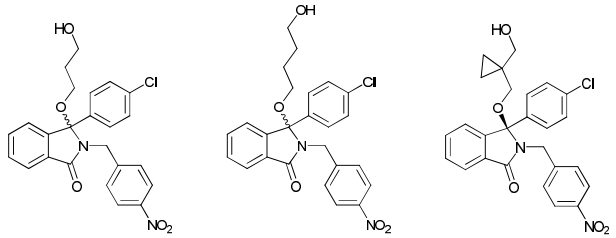
**Abstract**

The p53 tumour suppressor acts as 'the guardian of the genome' playing roles in cell cycle progression, DNA repair and apoptosis. In normal cells the activity of p53 is tightly regulated by the MDM2 protein via a negative feedback loop. Inhibition of the MDM2-p53 protein-protein complex is expected to reactivate normal p53 pathways in cells over-expressing MDM2, resulting in anti-tumour activity.




**NU8348** $IC_{50}$ = 532 ± 74 nM

**NU8349** $IC_{50}$ = 357 ± 44 nM

**NU8354A** $IC_{50}$ = 171 ± 5 nM

During our previous studies we have identified small molecule inhibitors of the MDM2-p53 interaction based on an isoindolinone scaffold, as exemplified by NU8348 and NU8349. Further optimisation has resulted in the elucidation of structure-activity relationships for the isoindolinone pharmacophore, and the identification of compounds with improved potency, including NU8354. Resolution of the enantiomers using chiral HPLC gave NU8354A ($IC_{50}$ = 171 ± 15 nM) and ($IC_{50}$ = 1.30 ± 0.11 μM). Further structure-activity studies are ongoing and the results will be presented. The cellular activities of key compounds have been demonstrated with dose-dependent induction of p53 regulated genes in a variety of model systems



# Solvent-free mechanochemical synthesis of aryl glycosides

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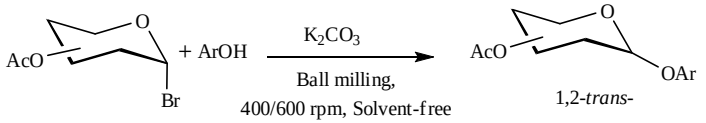
**Abstract—**

Aryl glycosides are of significant importance to both chemists and biologists due to their medicinal properties as well as their suitability for application as substrates in various enzyme assays and also due to their widespread occurrence in nature. A number of methods are available for their syntheses, but suffers from one or more drawbacks such as anomerization, orthoester formation, β-elimination and/or hydrolysis which finally lead to decrease in the yield and sterochemical outcome of the reaction.[1]




We have developed a highly efficient, sterospecific practical route for the synthesis of aryl β-glycosides under solvent-free conditions by mechanochemical procedure employing a planetary ball mill in excellent yield. The method requires no chromatographic purification or use of a phase-transfer catalyst. Several aryl glycosides have been synthesized from a range of readily available glycosyl halides following this procedure.[1]

**References**

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# Imidate Ligand Effects in Gold Mediated Catalysis

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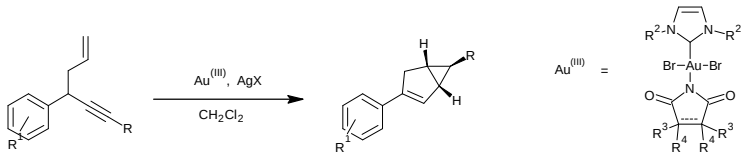
**Abstract**

There has been much recent interest in the catalytic properties of gold in synthetic chemistry.[1] Previously considered an inert element, gold can form highly reactive salts and complexes in the (I) and (III) oxidation states which have been shown to catalyse a wide range of atom economic and clean synthetic transformations under mild conditions, involving carbon-carbon unsaturated bonds.

This study relates to the first catalytic application of imidate ($[N(COR)_2]^-$) ligands in place of the ubiquitous halide ligands. The effect of these ligands on the efficiency of gold(III)-catalysed propargylic substitution[2] and enyne cycloisomerisation[3] reactions has been investigated.

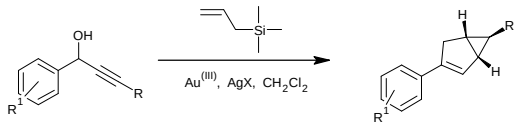
When activated by silver salts (to produce cationic complexes by the abstraction of bromide) these complexes emerge as efficient catalysts for the cycloisomerisation of 1,5-enynes to produce bicyclo[3.1.0]hexenes; key moieties in selected pharmaceutical targets (Scheme 1).




**Scheme 1.** Gold(III) catalysed cycloisomerisation of 1,5 enynes to produce bicyclo[3.1.0]hexenes.

The nature of the imidate ligand employed has a dramatic influence on the rate of reaction, highly electron-withdrawing imidates give significantly greater conversions than halide ligands. It was also found that the use of 'super' non-coordinating silver salts greatly accelerates the rate of reaction compared with more coordinating salts.

The high Lewis acidity of these Au(III) complexes has allowed the development of a unique tandem propargylic substitution-cycloisomerisation reaction which produces the bicyclic product in one-pot from propargylic alcohols and allyl silanes (Scheme 2). This novel process is not efficiently catalysed by any other known metal catalysts.




**Scheme 2.** Gold(III) catalysed tandem nucleophillic substitutiuon-cycloisomerisation of propargyl alcohols to produce bicyclo[3.1.0]hexenes.

**References**

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# Chemical Biology of Amyloid Formation

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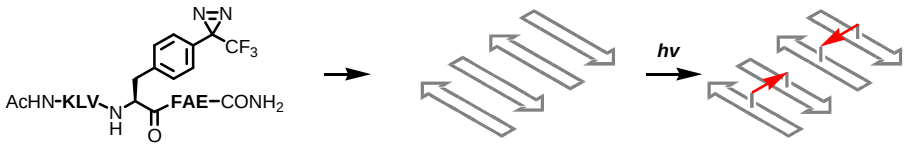
**Abstract**

The formation of amyloid fibrils is a characteristic of a number of human diseases, among them debilitating conditions such as Alzheimer's Disease.[1] Fibrils are extended homopolymeric $\beta$-sheet aggregates, of which the respective aggregating monomers can be quite diverse in their sequences and native fold. Fibril structures are interesting because their formation tends to be coincident with the onset of disease, and because they represent the end-point product of a complex self-assembly process. It is becoming apparent, however, that oligomeric intermediates implicated in this process are perhaps the true aetiological link to the disease state[1]; thus, it is of interest to isolate and study them. This endeavour is challenging because the intermediates are metastable and they occur in mixtures. Our laboratory is developing a covalent capture strategy to circumvent these problems. In this strategy, a photolabile group is introduced into the aggregating monomer using side-chain-functionalised Fmoc amino acids and solid phase peptide synthesis. The photolabile group is designed to form a strongly alkylating intermediate upon irradiation with ultraviolet light. Thus, irradiation of a supramolecular assembly generates covalent cross-links *in situ*, providing a "snapshot" of the self-assembly process.

Our model system employs a seven-residue fragment of the amyloid $\beta$-peptide (residues 16–22, "A$\beta_{16\text{-}22}$"; sequence = AcNH-KLVFFAE-$CONH_2$), which is known to form in-register antiparallel $\beta$-sheet fibrils at pH 7.4 (ref. 2). Functionalisation of A$\beta_{16\text{-}22}$ can be achieved *via* the substitution of one or both of the Phe residues with tfmd-Phe, an analogue containing a photolabile diazirine ring.[3]




Peptide containing tfmd-Phe | Self-assembled β-sheet | Irradiation forms cross-links

As a proof of principle, we are testing our strategy on fibrils of A$\beta_{16\text{-}22}$. It was shown in earlier work that A$\beta_{16\text{-}22}$ containing tfmd-Phe at residue 19 could form fibrils, and irradiating these fibrils yielded covalent dimers that were detectable by mass spectrometry.[4] We anticipate that further substitutions will allow us to cross-link more extensive structures, and that the approach will be applicable to the trapping of metastable intermediates. We have also incorporated other photolabile amino acids into A$\beta_{16\text{-}22}$, namely the 4-benzoyl and 4-azido analogues of L-phenylalanine. Although the precision of cross-linking mediated by these functionalities is known to be lower than that of tfmd-Phe, we anticipate that they will complement our existing results, and allow us to further explore the tolerance of amyloid structures to unnatural amino acids.

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# Novel Transannelation Studies Towards Pinguisane-type Sesquiterpenoids

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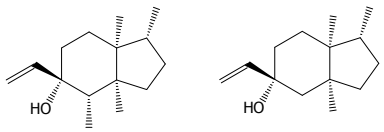
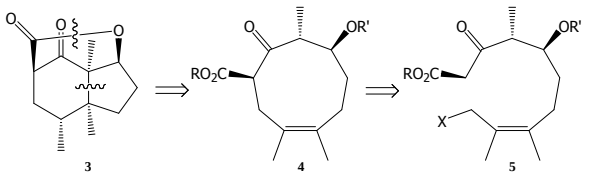
The construction of polycyclic ring systems *via* transannelation chemistry has been reported in numerous natural product syntheses. [1] Transannelation reactions have proved to be a powerful tool, their efficient but elegant nature allowing rapid access to elaborate intermediates. This poster will describe studies towards the pinguisane-type sesquiterpenoids, particularly (+)-pinguisenol **1** and (+)-normethylpinguisenol **2**. Such compounds have been isolated over the last 50 years from a range of liverworts [2] and have shown impressive activity as **antibiotics** and **anti-cancer** agents.[3,4]



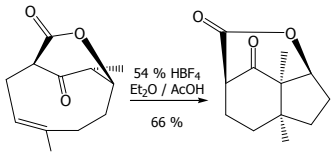

**1** **2**

The assembly of the bicyclo[4.3.0]nonane core **3** will employ two key steps; firstly an intramolecular Pd $\pi$-allyl ring closure, or more simply an $S_N2$ displacement of an allylic bromide to form a 9-membered ring **4**. Secondly a **Brønsted acid** promoted transannular cyclisation of an enol onto an unactivated carbon–carbon double bond to furnish the core of the pinguisane system. [5]




**3** **4** **5**

Previous [5] and current work has shown that treatment of the lactone **6** with $HBF_4$ in acetic acid provided the bicyclic core in good yield. Further elaboration of the lactone **7** to (+)-normethylpinguisenol **2** and attemts towards (+)-pinguisenol **1** following a similar route are anticipated.




**6** **7**

**References**

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# Studies Towards Total Synthesis of Viridenomycin

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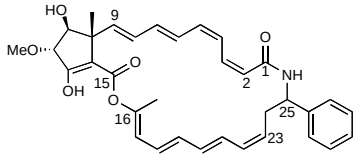
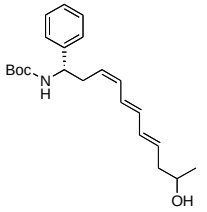
**Abstract**

Viridenomycin (**1**) was first isolated from the culture broth of *Streptomyces viridochromogenes* strain No. T-24146 in 1975 as a weakly acidic and lipophilic substance, which showed strong inhibitory activity against *Trichomonas vaginalis* and gram-positive bacteria.[1] In 1991, this compound was isolated from the culture broth of *Streptomyces gannmycicus* as an agent for prolongation of the survival periods of mice infected with B16 melanoma.[2] The structure of viridenomycin was established except for the absolute configuration and the relative configuration at C-25.[3] It consists of a fully substituted cyclopentene ring, a phenyl group and 24-membered macrocyclic polyene lactam.[4]




**1**

In this presentation, we will discuss the synthesis of *tert*-butyl (1*R*,3*Z*,5*E*,7*E*)-10-hydroxy-1-phenylundeca-3,5,7-trienylcarbamate **2** as an important step towards the synthesis of the southern polyene part of Viridenomycin **1**.




**2**

**References**

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# Tandem Retro-Aldol/ Olefination/ Michael Addition Cascade Processes

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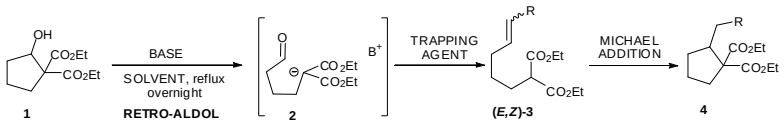
**Tandem Chemistry: An overview.**

In recent years, the advantages of *Domino*, or *Tandem*, chemistry have become widely recognised.[1, 2] The cost-time benefits and reduced environmental impact are probably the greatest advantages of this chemistry. *Tandem* chemistry has been a subject of study in the Taylor group for the past few years. Interesting and challenging chemistry has been developed with several applications in natural product synthesis.[3]

**Studies towards the tandem Retro-Aldol/ Olefination/ Michael addition reactions of alcohols.**

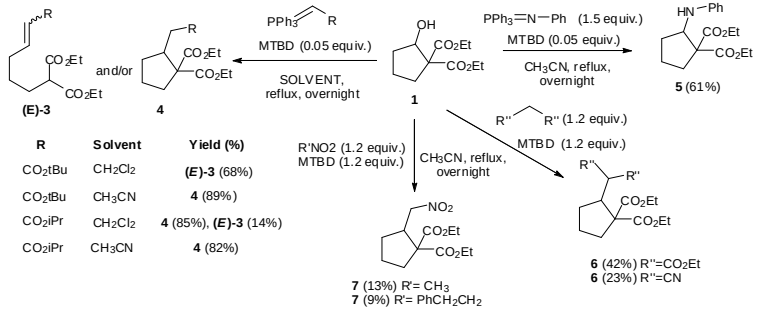
As a general idea, our strategy involves the retro-aldol reaction of substrate **1** to give aldehyde **2**, which can be trapped *in situ* with an olefinating reagent to afford alkene **3**. Under basic conditions, this can undergo a further intramolecular Michael addition to give cyclic ester **4**.




Four different trapping reactions were tested: **Wittig olefination, Aza-Wittig imination, the Henry reaction and Knoevenagel condensation.**

Generally, 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD) was found to be the optimal base, affording high yields when used both in stoichiometric and catalytic amounts.

Successful results were achieved with all four trapping reactions demonstrating the scope of this novel strategy. High product selectivity was observed especially when Wittig olefination was used as a trapping reaction.




| R | Solvent | Yield (%) |
|---|---|---|
| $CO_2tBu$ | $CH_2Cl_2$ | **(*E*)-3** (68%) |
| $CO_2tBu$ | $CH_3CN$ | **4** (89%) |
| $CO_2iPr$ | $CH_2Cl_2$ | **4** (85%), **(*E*)-3** (14%) |
| $CO_2iPr$ | $CH_3CN$ | **4** (82%) |

Recent studies have also proved this tandem process to be successful with cyclic substrates containing different electron withdrawing groups, as well as with heterocyclic and monoactivated substrates.

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# Direct Amide Formation between Carboxylic Acids and Amines

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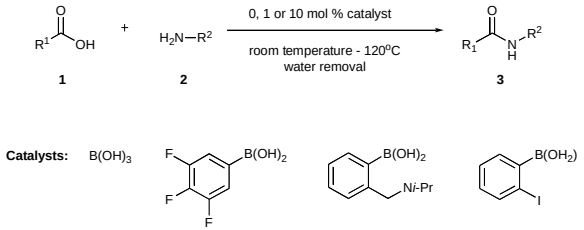
**Abstract**

Amide bonds are generally formed from amines and carboxylic acid derivatives such as acyl halides, anhydrides, or coupling reagents such as carbodiimides.[1] However, the most desirable way of making amides is via direct formation between amines and carboxylic acids. Direct amidation has been known since 1858 but is generally regarded as impossible due to the formation of an unreactive ammonium-carboxylate salt. Since amide formation is an important industrial chemical reaction there is a major need to develop a clean and efficient process under ambient conditions and in this area boron based compounds have shown promise.[2-5]




**Scheme 1.** General equation for direct amide formation and catalyst structures.

This work aims to further investigate the use of boronic acid catalysts and to carry out thorough mechanistic and kinetic studies for direct amide formation, both catalysed and uncatalysed, which is so far unexplored. This work will also improve on the design and synthesis of new catalysts (chiral and achiral) for achieving direct amide formation under ambient conditions and in the most environmentally friendly solvent conditions. The major challenge of this work is to provide the chemical community with a comprehensive understanding of the direct amide formation reaction, which will lead to an appreciation of why some boronic acid catalysts are better than others.

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# The Telescoped Intramolecular Michael/Olefination (TIMO) Approach to α-Alkylidene-γ-butyrolactones.

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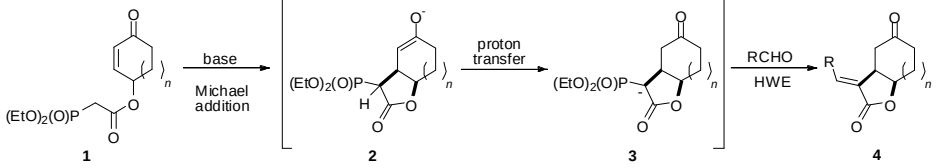
As part of our growing interest in tandem or telescoped processes, we have designed a one-pot approach to α-alkylidene-γ-butyrolactones in which the moiety of interest is installed in a telescoped intramolecular Michael (anion-exchange) olefination sequence (Scheme 1).

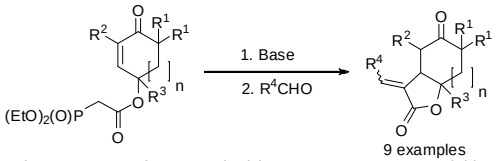



Scheme 1: TIMO approach to α-alkylidene-γ-butyrolactones.

Initial optimisation studies were performed on phosphonoacetate **1** (n = 1) derived from the corresponding γ-hydroxyenone and commercially available diethyl phosphonoacetic acid. KO*t*-Bu in THF proved to be the best base/solvent combination and paraformaldehyde was the optimal formaldehyde source. The α–methylene-γ-butyrolactone lactone product **4** (R = H, n = 1) was found to be highly base-sensitive. The use of a substoichiometric quantity of base (0.95 equiv) afforded product **4** in 77% yield.

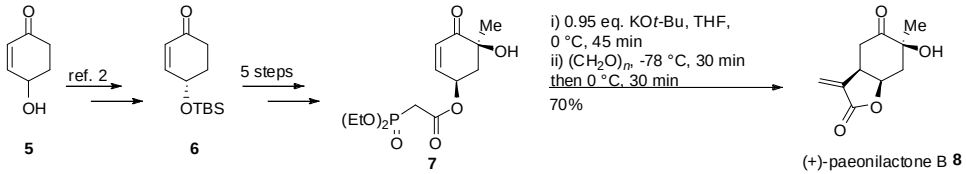
Subsequent to our initial success, we investigated the scope of the TIMO sequence in terms of both the aldehyde and enone components (Scheme 2).

KHMDS was found to be the optimal base when the TIMO cascade was performed with aromatic aldehydes, presumably due to the competing Cannizzaro reaction.



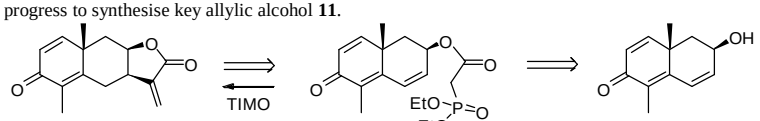

Scheme 2: Scope of TIMO methodology.

With the methodology study complete, our attention turned to a suitable natural product synthesis. Paeony root has a history of use in Chinese and Japanese medicine as an analgesic and, in 1985, paeonilactone B **8** was isolated from *paeonia albiflora pallas*.[1] It has been prepared previously in both racemic and optically pure (+) enantiomer forms.




Scheme 3: Synthesis of (+)-paeonilactone B

After publishing our initial communication,[3] we identified yomogin **9** as a suitable target to extend our methodology with a 1,6-conjugate addition (Scheme 4). The natural product exhibits potent anti-cancer biological activity and was isolated in 1966 from *artemisia princeps*,[4] a perrenial member of the daisy family with a history of use in oriental medicine. Work is currently in progress to synthesise key allylic alcohol **11**.




Scheme 4: RSA of yomogin

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# Design, Synthesis and Evaluation of New Bacterial Inhibitors

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## Abstract

Bacterial resistance presents a serious global threat to health, and threatens to undermine much of the work of the last 50 years which has lead to the current spectrum of antibiotics.[1] There is, therefore, an urgent need for the identification of new bacterial targets as well as new classes of antibiotics. Classical approaches to the identification of new drugs include the use of analogues based on established classes. However, the resistance mechanisms for these classes quickly evolve to render these derivatives ineffective.[2] New classes of antimicrobial agents are therefore needed which do not share this cross-resistance.

Structure based ligand design is a new approach to drug discovery replacing traditional methods of screening libraries of compounds (HTS).[3] SPROUT is a general purpose program for the design of small molecule inhibitors.[4] Using this *de novo* approach, recent efforts into the design of novel inhibitors of RNA polymerase (RNAP) target the Myxopyronin (Myx) binding region. This target site is located in a different region of the enzyme to that involved in the binding of the drug Rifampicin (Rif), where increased resistance to Rif presents a problem in the treatment of such diseases as Tuberculosis. A series of compounds based on an initial SPROUT hit has been synthesised and their biological evaluation ongoing.

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# A New and Efficient Synthesis of Alkynyliodonium Salts

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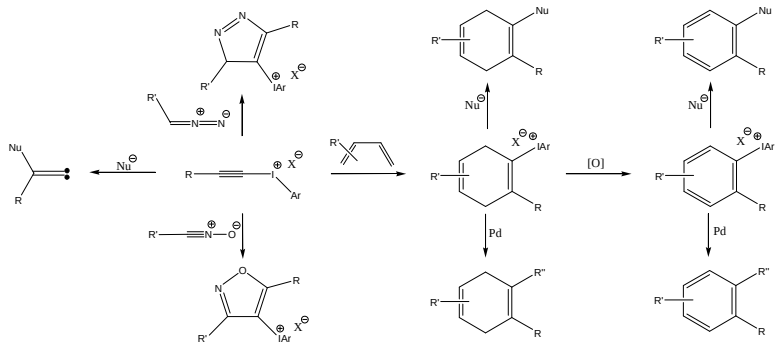
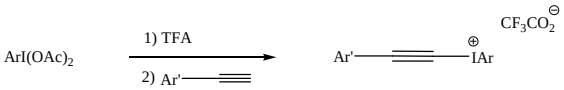
Previously, syntheses have been reported for alkynyliododonium mesolates, triflates, tosylates and tetrafluoroborates.[1] These syntheses often require hard to prepare or unstable starting materials and produce products which are difficult to purify and often unstable. To date there have been no comprehensive, comparative studies on the formation of alkynyliodonium salts.

The strongly electron withdrawing iodonium group makes alkynyliodonium salts highly reactive towards 1,3-dipoles, Diels-Alder and Michael-type conjugate addition as well as being useful sources of carbenes.[2] These carbenes provide access to a wide range of aromatic and aliphatic ring systems.[3]



Through variation of both the alkynyl terminus group and the iodonium salt counter ion we have developed the first fast and efficient method for the synthesis of a range alkynyliodonium trifluoroacetate salts from commercially available and inexpensive starting materials.



| (Ar = Ph) Ar': | | (Ar' = Ph) Ar: | |
|---|---|---|---|
| 4-Bromophenyl | 66% | 4-Methylphenyl | 85% |
| 4-Pentylphenyl | 77% | 4-Chlorophenyl | 68% |
| Thiophen-3-yl | 61% | 4-Methoxyphenyl | 62% |
| 2,4,5-Trimethylphenyl | 54% | 2-Methoxyphenyl | 56% |
| | | Thiophen-2-yl | 65% |

These salts can be purified simply by recrystalisation and are stable in comparison to analogous triflate and tosylate salts allowing their scope as versatile intermediates to be determined for the first time.

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# Studies on the 1,2-Metallate Rearrangement of Carbohydrate Derivatives

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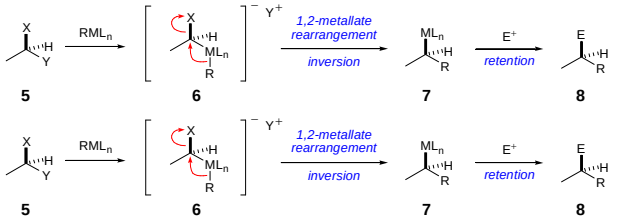
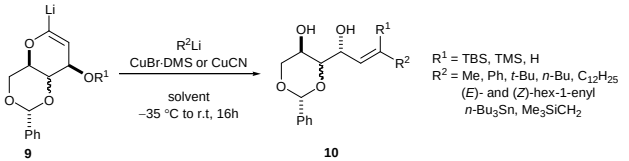
**Abstract**

1,2-Metallate rearrangements are useful carbon-carbon bond forming reactions, involving 1-hetero-1-alkenyl (**2**) or 1-hetero-1-alkyl (**6**) metallate complexes in which a carbon ligand R bound to a metal M undergoes a 1,2-shift to an electrophilic carbon attached to the same metal with inversion of configuration to give an alkenyl- or alkyl-metal product (**3** and **7**) (Scheme 1).[1], [2]



Scheme 1

The migrating ligand R can be alkyl, cyclopropyl, phenyl, alkenyl, $Me_3SiCH_2$ or $Bu_3Sn$, while the heteroatom leaving group can be a halogen, RO–, $R_2N(O)CO$–, RS–, $R_2S^+$–, $RSO_2$–. As substrates for 1,2-metallate rearrangement simple α-metallated vinyl ethers have been mostly used.[2] We developed a general methodology for the 1,2-metallate rearrangement of more advanced cyclic α-alkoxyalkenyl lithio cuprates. The reaction is an attractive method for alkene synthesis due to the availability of substituted dihydropyranes (e.g. from sugar derivatives). We explored the scope of the reaction using different lithiated glycals as substrates (**9**) and different ligands $R^2$ on copper (Scheme 2). The influence of the source of copper(I) (CuCN and $CuBr{\cdot}SMe_2$) and the solvent were studied.



Scheme 2

Under optimized conditions a variety of alkenes **10** was prepared in good to excellent yields. This method for alkene synthesis can be considered general and possibly opens up new entries to many natural products. Efforts are under way to synthesize sphingosine derivatives from galactose, using a 1,2-metallate rearrangement as a key step.

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# Synthesis of *P*-Stereogenic Phosphines *Via* Asymmetric Lithiation

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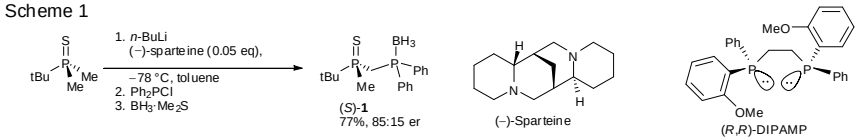
**Abstract**

The Nobel prize in chemistry was awarded to Knowles in 2001 for the development of Rh-catalysed enantioselective hydrogenation. This reaction was used in the asymmetric synthesis of L-DOPA and required the chiral diphosphine ligand (*R*,*R*)-DIPAMP. These ligands exhibit high substrate specificity and there is therefore a requirement for asymmetric methodology which can generate a diverse range of chiral phosphines.

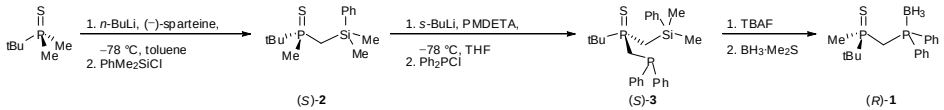
The enantioselective lithiation of dimethylphosphine boranes and sulfides can be achieved using butyllithium in the presence of (−)-sparteine.[1] This is a useful method for the asymmetric synthesis of P-stereogenic phosphines analogous to DIPAMP.[2,3] We have discovered that the deprotonation of phosphine sulfides can be performed using n-butyllithium and low loadings of (−)-sparteine (0.05 eq), maintaining excellent yield and high enantioselectivity in the reaction (Scheme 1).[4]

Scheme 1



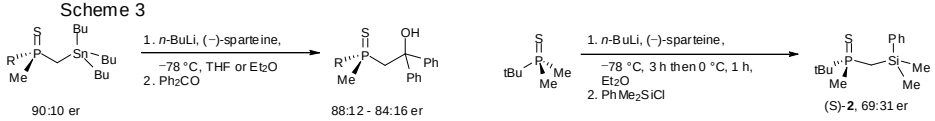

(+)-Sparteine is not easily available therefore accessing the opposite enantiomeric series presents a significant challenge. One route to these compounds utilises the regioselective lithiation of silylphosphine sulfide (*S*)-**2** at the methyl position and trapping with an electrophile (Scheme 2).

Scheme 2




We have observed that the lithiated phosphine sulfides are configurationally labile above −50 °C and the epimerisation process has been explored using transmetallation and temperature variation (Scheme 3). The results indicate the potential to perform enantioselective lithiation/trapping under dynamic-thermodynamic resolution conditions.

Scheme 3




In summary, three different approaches for the asymmetric synthesis of *P*-stereogenic compounds will be presented.

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# Total Synthesis of (−)-*N*-Acetylcolchinol

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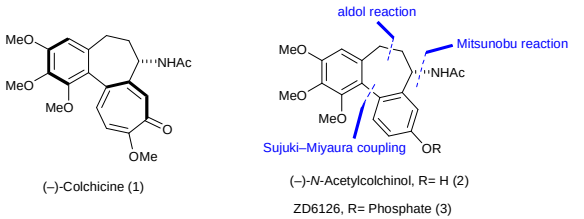
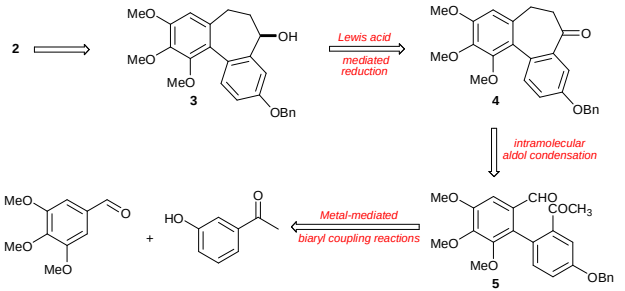
**Abstract**

Colchicine **1**, the major alkaloid of *Colchicum autumnale* (Meadow saffron), is an important bioactive compound known for its anti-mitotic properties and has been used in the treatment of acute gout and familial mediterranean fever for many years. Although colchicine was identified as an anticancer agent, its use has been limited due to the toxicity resulting in multi-organ failure and death ($LD_{50}$ = 1.6 mg kg )[1]. The search for colchicine analogues with improved therapeutic index lead to (a*R*,7*S*)-(–)-*N*-acetylcolchinol as a promising lead compound. Its water-soluble phosphate drug ZD6126 selectively induces tumour vascular damage and tumour necrosis at well tolerated doses.[2]




Herein, we describe an asymmetric synthesis of (–)-*N*-acetylcolchinol (NAC) based on a Suzuki–Miyaura coupling to generate the biaryl pharmacophore **5**. The sole asymmetric centre was introduced by an asymmetric reduction of a dibenzosuberone **4** using lithium borohydride in the presence of stoichiometric amounts of a chiral Lewis acid ($TarBNO_2$). Starting from commercially available compounds, 10 g of NAC were synthesized following this route.[3]

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# Single-Step Synthesis of *N*-Succinimidyl-4-[$^{18}$F]Fluorobenzoate

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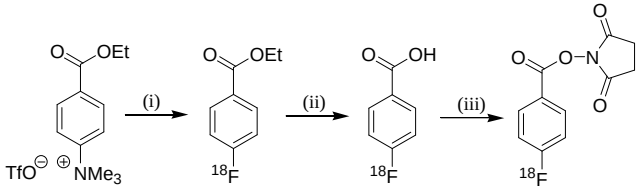
The application of the acylation approach with *N*-succinimidyl-4-[$^{18}$F]fluorobenzoate ([$^{18}$F]SFB) is the most versatile method for the incorporation of $^{18}$F into peptides, proteins or antibodies. However the radiosynthesis of [$^{18}$F]SFB requires a laborious three-step procedure, which limits its utilization.[1] Therefore there is major need for an improved radiosynthetic method.

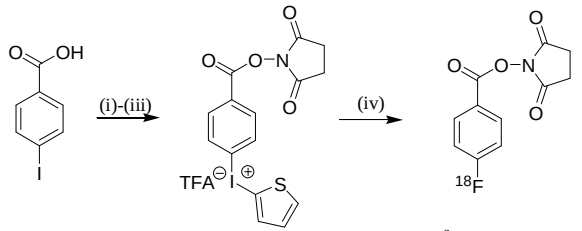
**Scheme 1**




(i) $K^{18}F/K_{2.2.2}$; (ii) $NaOH/H_2O$; (iii) coupling reagents (DCC, DSC or TSTU).

Diaryliodonium salts have been shown to be suitable precursors for single-step nucleophilic [$^{18}$F]fluorination of arenes without the need of further activating groups. It was then of interest to use this approach for the radiosynthesis of [$^{18}$F]SFB, in particular salts containing the 2-thienyl group which, in this case, enables highly regioselective [$^{18}$F]fluorination. The required precursor of (4-((2,5-dioxopyrrolidin-1-yloxy)carbonyl)phenyl)(thiophen-2-yl)iodonium trifluoroacetate was synthesized in three steps with an un-optimised yield of 26%.[2, 3] The precursor was then subjected to [$^{18}$F]fluorination. Radio-HPLC analysis indicated that [$^{18}$F]SFB was formed in radiochemical yields of 13-23% (n = 4).

**Scheme 2**




(i) TSTU, TEA, DMF, 2 h, 82%; (ii) $(Bu_3Sn)_2$, $Pd(PPh_3)_4$, PhMe/DMF, Δ, 24 h, 48%;[3] (iii) diacetoxyiodo-2-thiophene, TFA, $CH_2Cl_2$, -30 °C to R.T., 24 h, 26%; (i) $K^{18}F/K_{2.2.2}$, TEMPO, DMF, 5 min.

For the first time, a simple single-step method for the radiosynthesis of the prosthetic radiolabelling reagent [$^{18}$F]SFB has been developed. Optimisation of the technology is on-going.

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