Organic & Biomolecular Chemistry

An international journal of synthetic, physical and biomolecular organic chemistry

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IN THIS ISSUE

ISSN 1477-0520 CODEN OBCRAK 7(3) 401–612 (2009)

Cover

See Jens Bitzer *et al.*, pp. 444–450. *Streptomyces* as producer of novel Y-type actinomycins, new β-peptidolactones with strong cytotoxic and antibacterial bioactivities, as if proclaiming an 'anathema' on cancer cells as well as pathogens.

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CHEMICAL BIOLOGY

B9

Drawing together research highlights and news from all RSC publications, *Chemical Biology* provides a 'snapshot' of the latest developments in chemical biology, showcasing newsworthy articles and significant scientific advances.

Chemical Biology

February 2009/Volume 4/Issue 2

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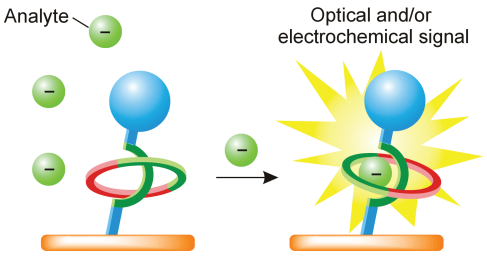
EMERGING AREA

415

Interlocked host rotaxane and catenane structures for sensing charged guest species *via* optical and electrochemical methodologies

Michał J. Chmielewski, Jason J. Davis* and Paul D. Beer*

Interlocked host molecules are demonstrated to exhibit high degrees of molecular recognition which, when coupled to appended reporter groups, make them highly promising candidates for the development of molecular sensors.



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Organic & Biomolecular Chemistry (print: ISSN 1477-0520; electronic: ISSN 1477-0539) is published 24 times a year by the Royal Society of Chemistry, Thomas Graham House, Science Park, Milton Road, Cambridge, UK CB4 0WF.

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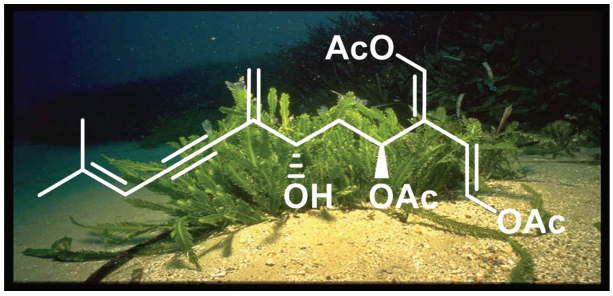
425

First total synthesis of (−)-caulerpenynol

Laurent Commeiras,* Jérôme Thibonnet and Jean-Luc Parrain*

The first diastereoselective synthesis of the antimicrobial and cytotoxic agent (−)-caulerpenynol **2** has been achieved in relatively few steps from the commercially available (*S*)-malic acid.

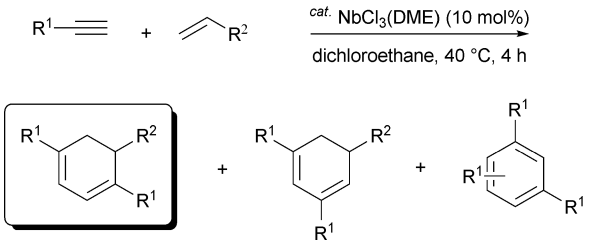


428

$NbCl_3$-catalyzed [2+2+2] intermolecular cycloaddition of alkynes and alkenes to 1,3-cyclohexadiene derivatives

Yasushi Obora,* Keisuke Takeshita and Yasutaka Ishii*

$NbCl_3$(DME)-catalyzed [2+2+2] intermolecular cycloaddition of alkynes and alkenes was successfully achieved to give 1,4,5-trisubstituted-1,3-cyclohexadiene derivatives in good yields.

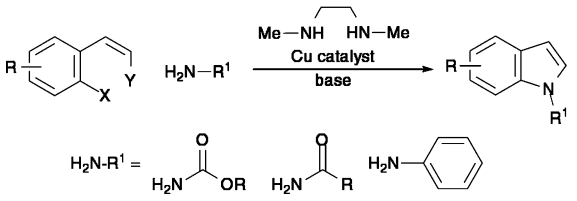


432

Tandem copper-catalysed aryl and alkenyl amination reactions: the synthesis of *N*-functionalised indoles

Roy C. Hodgkinson, Jurgen Schulz and Michael C. Willis*

A Cu-diamine complex effectively catalyses tandem C–N bond formation on 2-(2-haloalkenyl)-aryl halide substrates, to deliver a series of *N*-functionalised indoles. Anilines, amides and carbamates are all effective coupling partners under the developed conditions.

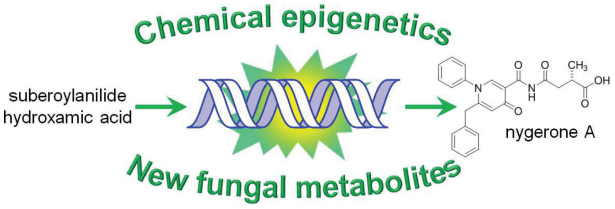


435

A chemical epigenetics approach for engineering the *in situ* biosynthesis of a cryptic natural product from *Aspergillus niger*

Jon C. Henrikson, Ashley R. Hoover, P. Matthew Joyner and Robert H. Cichewicz*

A cryptic fungal metabolite, nygerone A, was obtained from *Aspergillus niger via* chemical epigenetic modifier treatment.



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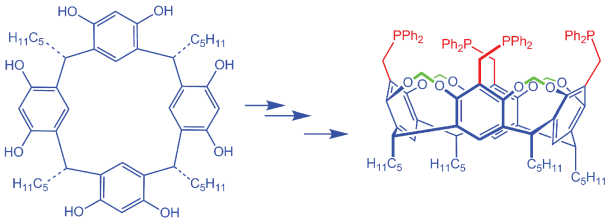
495

Synthesis of a resorcinarene-based tetraphosphine-cavitand and its use in Heck reactions

Hani El Moll, David Sémeril,* Dominique Matt,* Marie-Thérèse Youinou and Loïc Toupet

A straightforward, 7-step synthesis of the first tetraphosphine built upon a resorcinarene cavitand is described. The ligand was assessed in Heck coupling reactions.

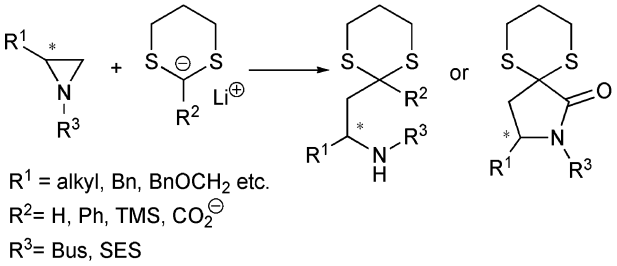


502

Ring-opening reaction of Bus- and SES-protected aziridines using lithiated dithianes

Ken Sakakibara and Kyoko Nozaki*

Bus- and SES-activated aziridines undergo an efficient ring-opening reaction with various lithiated dithiane anions to yield β-amino carbonyl equivalents, γ-lactam and *syn*- and *anti*-1,5-aminoalcohols.

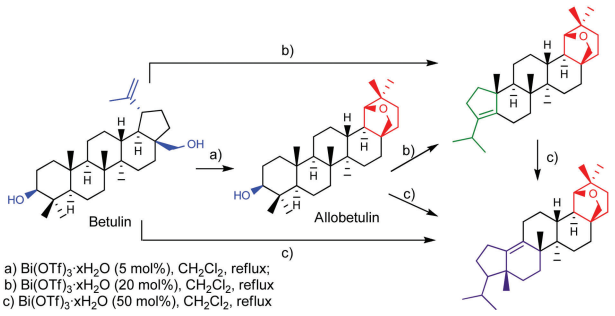


508

Bismuth triflate-catalyzed Wagner-Meerwein rearrangement in terpenes. Application to the synthesis of the 18α-oleanane core and A-*neo*-18α-oleanene compounds from lupanes

Jorge A. R. Salvador,* Rui M. A. Pinto, Rita C. Santos, Christophe Le Roux, Ana Matos Beja and José A. Paixão

The bismuth(III) salt-catalyzed Wagner-Meerwein rearrangement of terpenes is reported. 18α-Oleanane compounds bearing an additional O-containing ring are efficiently obtained from lupanes.

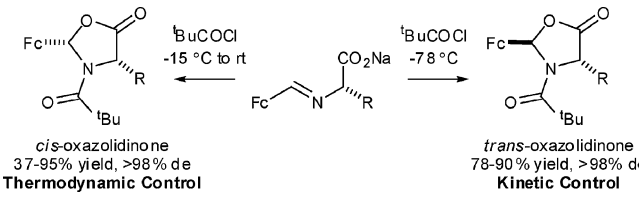


518

Kinetic and thermodynamic control in the stereoselective formation of *trans*- and *cis*-2-ferrocenyl-3-pivaloyl-4-alkyl-1,3-oxazolidin-5-ones

Francisco Alonso, Stephen G. Davies,* Almut S. Elend and Andrew D. Smith

A range of ferrocenylimines can be cyclised under kinetic control (−78 °C) or thermodynamic control (−15 °C to rt) to afford either pure *trans*- or pure *cis*-1,3-oxazolidin-5-ones, respectively.



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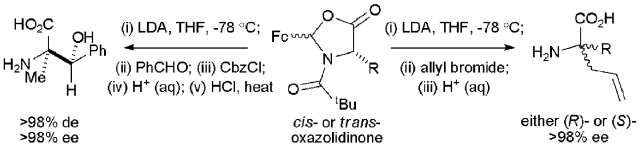
527

Stereoselective functionalisation of *cis*- and *trans*-2-ferrocenyl-3-pivaloyl-4-alkyl-1,3-oxazolidin-5-ones: asymmetric synthesis of (*R*)- and (*S*)-2-alkyl-2-aminopent-4-enoic acids and (2*R*,3*S*)-2-amino-2-methyl-3-hydroxy-3-phenylpropanoic acid

F. Alonso, S. G. Davies,* A. S. Elend, M. A. Leech, P. M. Roberts, A. D. Smith and J. E. Thomson

An efficient asymmetric synthesis of α,α-disubstituted-α-amino acids is presented.

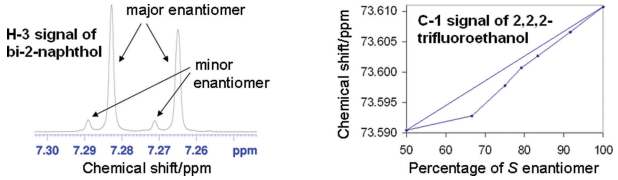


537

NMR and molecular modeling of the dimeric self-association of the enantiomers of 1,1′-bi-2-naphthol and 1-phenyl-2,2,2-trifluoroethanol in the solution state and their relevance to enantiomer self-disproportionation on achiral-phase chromatography (ESDAC)

Ville Nieminen, Dmitry Yu. Murzin and Karel D. Klika*

Modeling of 1,1′-bi-2-naphthol, which shows classic SIDA behavior, and 1-phenyl-2,2,2-trifluoroethanol, for which NMR signals migrate unsplit, has been conducted in light of the ESDAC phenomenon.

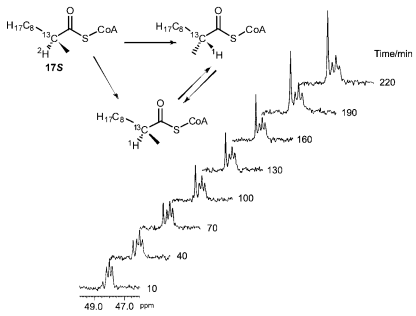


543

Synthesis and use of isotope-labelled substrates for a mechanistic study on human α-methylacyl-CoA racemase 1A (AMACR; P504S)

Daniel J. Darley, Danica S. Butler, Samuel J. Prideaux, Thomas W. Thornton, Abigail D. Wilson, Timothy J. Woodman, Michael D. Threadgill and Matthew D. Lloyd*

The reaction mechanism of human recombinant α-methylacyl-CoA racemase was studied using labelled substrates. Chiral inversion can occur in both directions with an equilibrium constant of 1.09 ± 0.14.

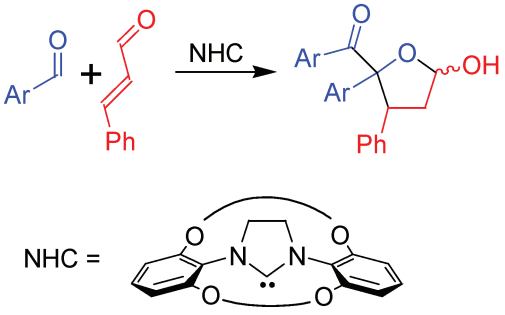


553

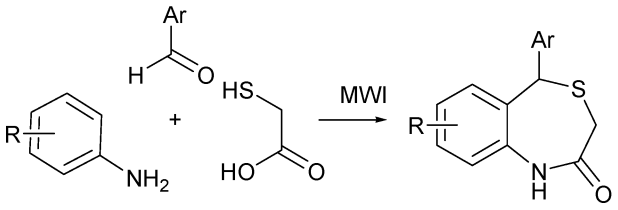
Organocatalysis by bimacrocyclic NHCs: unexpected formation of a cyclic hemiacetal instead of a γ-butyrolactone

Ole Winkelmann, Christian Näther and Ulrich Lüning*

A concave NHC catalyzes the reaction of a benzaldehyde with an enal to give a hemiacetal instead of Stetter products or lactones.



557

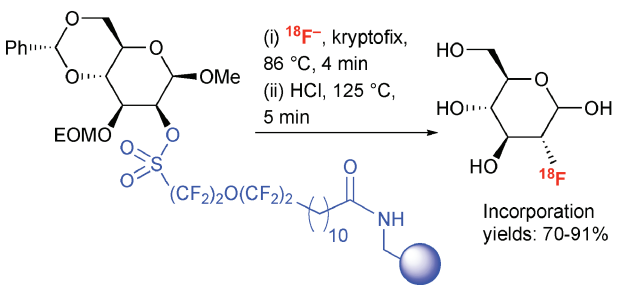


An efficient and chemoselective synthesis of benzo[*e*][1,4]thiazepin-2(1*H*,3*H*,5*H*)-ones *via* a microwave-assisted multi-component reaction in water

Shu-Jiang Tu,* Xu-Dong Cao, Wen-Juan Hao, Xiao-Hong Zhang, Shu Yan, Shan-Shan Wu, Zheng-Guo Han and Feng Shi

A new and efficient strategy for the synthesis of benzo[*e*][1,4]thiazepin-2(1*H*,3*H*,5*H*)-ones *via* a microwave-assisted multi-component reaction in aqueous media is described.

564

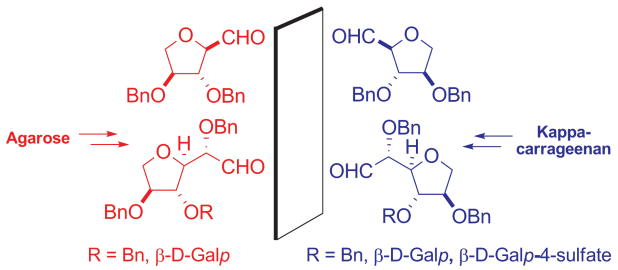


Synthesis of the positron-emitting radiotracer [^{18}F]-2-fluoro-2-deoxy-D-glucose from resin-bound perfluoroalkylsulfonates

Lynda J. Brown, Nianchun Ma, Denis R. Bouvet, Sue Champion, Alex M. Gibson, Yulai Hu, Alex Jackson, Imtiaz Khan, Nicolas Millot, Amy C. Topley, Harry Wadsworth, Duncan Wynn and Richard C. D. Brown*

A new approach to the radiosynthesis of 2-fluoro-2-deoxy-D-glucose (FDG) is described, starting from polymer-supported perfluorosulfonate ester precursors.

576

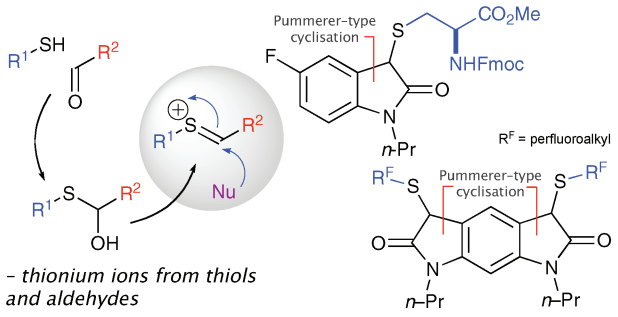


Production of carbohydrate building blocks from red seaweed polysaccharides. Efficient conversion of galactans into *C*-glycosyl aldehydes

Diogo R. B. Ducatti, Alessandro Massi,* Miguel D. Noseda, Maria Eugênia R. Duarte and Alessandro Dondoni*

The semisynthesis of two sets of *C*-glycosyl aldehydes (carbohydrate building blocks) with L- and D-configuration from natural polysaccharides agarose and kappa-carrageenan is described.

589



Formation of *N*-heterocycles by the reaction of thiols with glyoxamides: exploring a connective Pummerer-type cyclisation

Marc Miller, Johannes C. Vogel, William Tsang, Andrew Merrit and David J. Procter*

The reaction of thiols with glyoxamides provides a convenient method for the generation of thionium ions and the initiation of Pummerer-type reactions. The utility of the process has been illustrated in a synthesis of the indoloquinoline natural product, neocryptolepine.

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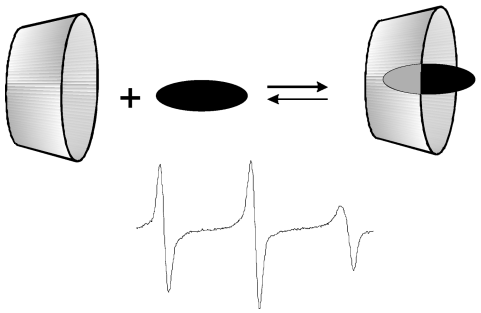

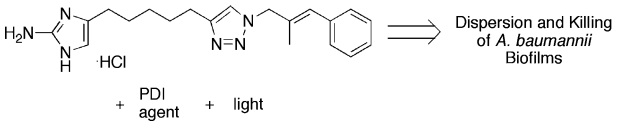

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Chemical Biology

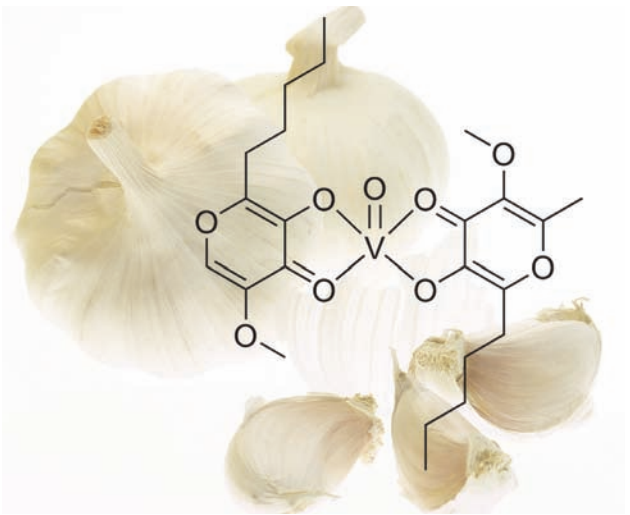
Extensive study looks at how vanadium complex affects glucose metabolism

Injection-free treatment for diabetes?

A compound found in garlic is the basis of a potential orally-available drug candidate for types 1 and 2 diabetes.

Diabetes incidence is increasing worldwide, and there is a continuing need to develop effective treatments. Exisiting treatments involve either injection with insulin (primarily for sufferers of type 1 diabetes), or treatment with drugs (for type 2 diabetes). However, says Hiromu Sakurai, of the Suzuka University of Medical Science, Japan, neither method is ideal, as they involve frequent injections, and the drugs have undesirable side-effects.

In earlier work, Sakurai's group had shown that a complex of vanadium and allixin, a compound found in garlic, lowered blood glucose levels in mouse models of both types 1 and 2 diabetes and that the effect was maintained for type 2 model mice given the complex orally. In its latest study the team found that the orally administered complex also lowered glucose levels in type 1 model mice, offering hope for an injection-free treatment for people with type 1 diabetes.



The vanadyl complex of garlic-compound allixin lowers blood glucose in diabetes models

The new study looked primarily at how the allixin complex works. By examining the effects of the complex on genes affected by diabetes, the researchers found that it activates not only the insulin signalling cascade, which regulates glucose metabolism, but also an enzyme that helps cells to absorb glucose.

John McNeill is a professor emeritus in the division of pharmacology and toxicology at the University of British Columbia, Vancouver, Canada. He says that although other vanadium compounds have shown promise for the treatment of diabetes, this investigation is extensive and 'adds significant information to our understanding of how vanadium compounds can affect both carbohydrate and lipid metabolism.'

The researchers say that the allixin and similar complexes could be good candidates for treating both type 1 and type 2 diabetes. Future work, says Sakurai, will be aimed towards clinical trials of their complexes in human diabetes patients.

David Barden

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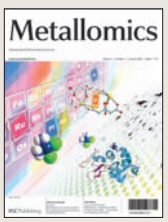
In this issue



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Research highlights

Studies reveal what makes stem cells change and how to make them stay the same

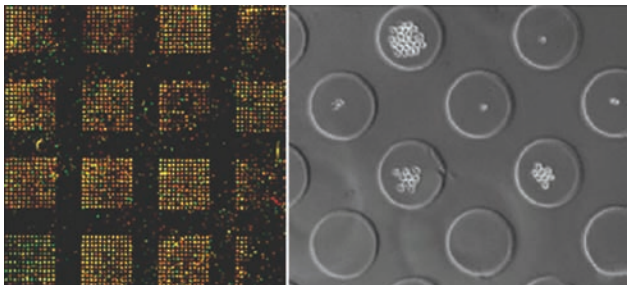
A different approach to stem cell research

Two recent papers published in RSC journal *Integrative Biology* highlight new details about adult stem cells.

John Connelly of the Wellcome Trust Centre for Stem Cell Research at the University of Cambridge, UK, describes the approaches used by the research teams as representing 'an exciting new direction in the field of stem cell biology.'

We all have stem cells which, localised in niches throughout the body, provide cells throughout our lifetimes. However, whilst stem cells have been used to replace and repair damaged tissue, very little is known about how the cells can do this. Understanding how stem cells convert into different cell types is important for the field of stem cell therapeutics to develop.

A group at the Lawrence Berkeley National Laboratory, US, led by Mark LaBarge and Mina Bissell, has teamed up with a group at the Panum Institute in Copenhagen, Denmark, to investigate human mammary stem cells, which can become any type of breast tissue. Meanwhile, Matthias Lutolf and a team at Stanford University School of Medicine, US, have investigated hematopoietic (blood forming) stem cells (HSCs) in adult mice.



Microarray technology was used to study stem cells held in many different environments

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The two teams used microarray technologies to study the stem cells. The aim for both groups was to establish how and why these cells specialise into different cell types and using arrays allowed them to conduct many experiments simultaneously. Working on the hypothesis that a stem cell's behaviour is instructed by its surroundings, the groups created model environments to mimic the complex microenvironment that stem cells inhabit within the adult body. This allowed them to investigate how the environment influences stem cells to change and could lead to ways of influencing stem cell function outside of the body.

Bissell and LaBarge's group used their microarrays to expose stem cells to many different proteins and biological molecules in 8000 different combinations. The group was able to identify which conditions led the cells to convert into different breast cell types, including luminal epithelial cells, cells that can become cancerous. They were also able to suggest which components would keep the cells in their original, unspecialised state. Bissell says that she hopes that this type of approach 'will teach us how to direct stem cell function in a therapeutic setting and possibly to reprogram non-stem cells to acquire other stem cell fates.'

Lutolf's group, by contrast, exposed the stem cells to a more limited set of molecules but used microwell arrays to allow them to view individual cells as they specialised. They were able to identify key regulators in maintaining the HSCs as stem cells. Lutolf says that these findings could be very valuable for scientists struggling to grow HSCs in the lab. 'These cells do not replicate without rapidly differentiating in vitro,' he adds. He explains that culturing stem cells in vitro would be 'a very important achievement because cultures of HSCs that could maintain their characteristic properties of self renewal could provide an unlimited source of cells for therapeutic transplantation.'

Laura Howes

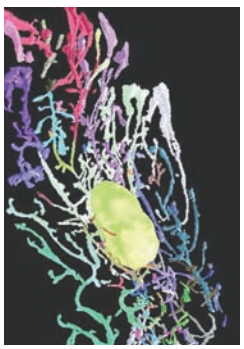
...whilst a microscopy platform maps stem cell reservoirs in mammary glands

Image analysis finds a niche

Scientists have linked different technologies to locate stem cell reservoirs in tissue.

During pregnancy the mammary gland goes through changes which suggest the tissue contains a reservoir of undifferentiated cells – cells that can convert into more specialised types. 'The question is: where are these stem cells located?' asks Mary Helen Barcellos-Hoff from Lawrence Berkeley National Laboratory, US, who led the team behind the research.

The researchers from the US and Spain built a computational microscopy platform that integrates image acquisition, storage, processing and allows them to analyse images of cells in tissue statistically. This approach makes it possible to look at cell populations at different scales – from the whole organ to tissue details and the single cell – which the researchers hope will allow them to understand how cells are affected by different microenvironments within the same tissue.



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The team used the method to look at the architecture of mouse mammary glands, widely used as a biological model for the human equivalent, explains Barcellos-Hoff. Her group labelled cells in the mammary glands of mice going through puberty. By monitoring the location of the label in cells in images from the same mice in adulthood and applying the statistical analysis, they were able to identify reservoirs of undifferentiated cells.

Jeffrey Rosen is an expert in mammary gland biology at Baylor College of Medicine, Houston, US, and welcomes the research. 'Being able to identify and localise label-retaining cells using a computational microscopy platform represents a major advance in the field,' he says. 'This important new approach should help in identifying and characterising the mammary stem cell niche in the three dimensional context of the mammary gland.' *Russell Johnson*

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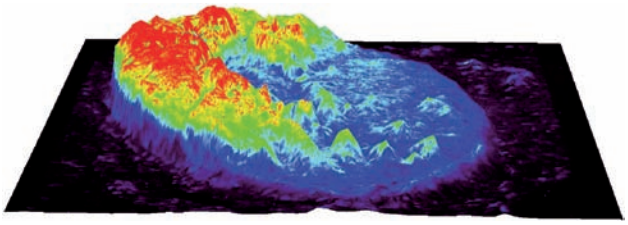
Mass spectrometry maps metastatic melanomas in lymph nodes

Detecting cancer on the move

Scientists are looking to the elements to detect cancer cells before they spread. Philip Doble from the University of Technology in Sydney and colleagues in Australia and the US have used a mass spectroscopy imaging technique to map skin cancer cells in human tissue. The method measures phosphorus concentrations as a diagnostic tool for metastatic melanoma.

Melanomas are malignant tumours which it has been estimated took in excess of 65 000 lives in 2000. The tumours are found predominately in skin but spread – metastasise – through the lymphatic system, making mapping this spread imperative. Nodes in the lymphatic system can act as filters to trap foreign particles and so often trap cancerous cells on the move. Approximately 20 per cent of melanoma patients have these cells in their lymph nodes, so it is a good place for scientists to look for early diagnosis.

Doble uses a mass spectroscopy technique called elemental bio-imaging to measure the trace element concentrations in cells. As altered levels of trace elements, such as phosphorus and sulfur, have long been associated with malignancy, the technique allows Doble and his team to identify cancerous cells by constructing maps of single (or ratios of) elements. In this way, they were able to provide clear images of a melanoma tumour in a lymph node and its boundary with the neighbouring healthy tissue.



Imaging phosphorus concentration provides a clear outline of a melanoma tumour in a lymph node

The severity of melanoma is usually identified by using a surgical procedure to carry out lymph node biopsies to determine how far the cancer has spread, then staining and examining the cells under a microscope. If cancer cells are found, the patient will have all the surrounding lymph nodes surgically removed to prevent the cancer spreading. Doble's method uses a much less invasive procedure, which extracts the lymph node biopsy samples with a needle.

Joanna Peak, science information officer at Cancer Research UK, says 'this study highlights the potential for developing new imaging methods that could improve detection of cancer spread. If these findings are developed further and evaluated more fully in the clinic they could lead to a less invasive and more efficient method for identifying melanomas that have spread by the time of diagnosis.'

Whilst in this case the team monitored phosphorus, sulfur and zinc levels and ratios, Doble suggests that the method also has the potential to image and analyse diseases in which other elements are known to play a role. 'Trace elements such as copper, zinc and iron are implicated in the progression of many neurological disorders such as Parkinson's and Alzheimer's disease,' he says. *Emma Shiells*

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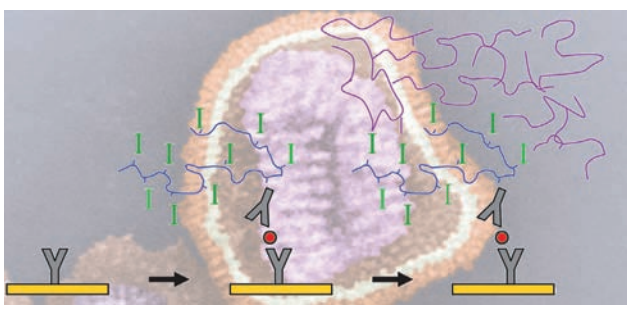
Light triggered polymer formation gives positive test for flu

Spotting the flu virus

US chemists can now 'see' if patients have the flu. Identifying the virus in infected patients could become much quicker and easier if a test developed by Chris Bowman at the University of Colorado in Boulder and colleagues becomes commercially available.

'Respiratory symptoms are very general,' says team member Hadley Sikes. 'So having a rapid, inexpensive way to rule out or confirm (and subtype) influenza is valuable, especially if the device is simple enough to be used anywhere and the results reliable,' she adds. 'Catching the spread of infections caused by particularly virulent flu strains early could help prevent a pandemic.'

Bowman's detector is a biosensor which has specific flu antibodies attached to part of its surface. When a mixture of flu virus lysate and a detecting reagent is placed on this surface and exposed to light, the antibody-coated areas become visible to the naked eye. The sensor works because virus proteins in the lysate attach to the antibodies on the surface. Since the detecting reagent contains both flu antibodies and light-sensitive molecules it also recognises and binds to the flu proteins if they are present and then, when exposed to light, forms hydrogel polymers which are visible. If no flu proteins are present, no reaction takes place and the test is negative. 'Of course, the real measure of whether the test has potential will come only after it is used successfully with real patient samples,' says Sikes.



Bowman's antibody-coated biosensor detects flu virus proteins (red) using a detecting reagent containing antibodies and light-sensitive molecules

Aaron Wheeler, whose team at the University of Toronto, Canada, works towards developing lab-on-a-chip devices for bioanalysis, describes the technology as 'really exciting' because results can be read unaided, by the human eye. 'Until now, many of the technologies being developed for point-of-care diagnostics required dedicated readers for analysis,' he says. 'This exciting new development could have a significant impact on this important problem.'
Janet Crombie

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MRI tracks anticancer drug across the blood–brain barrier

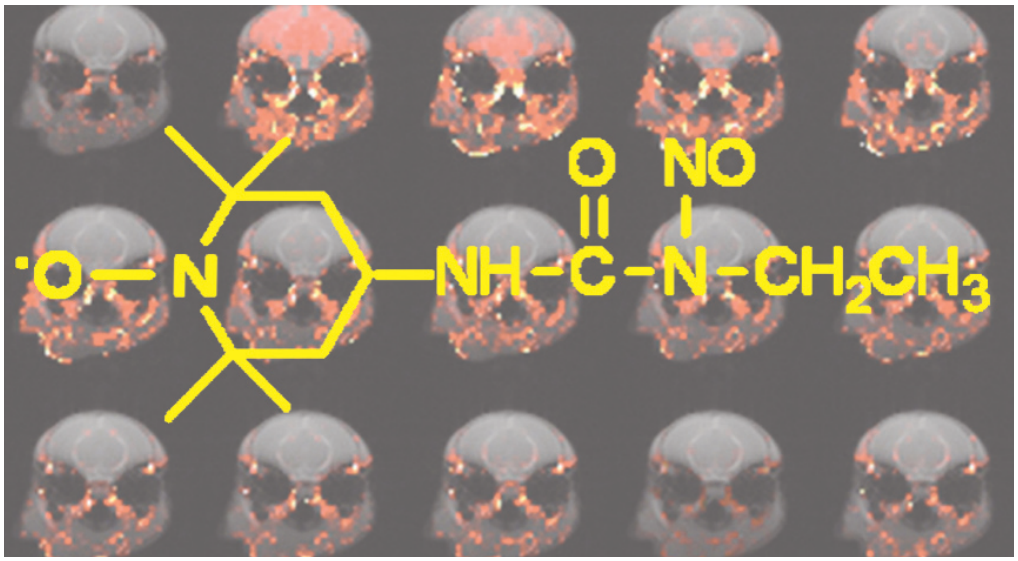
Following drugs into the brain

An international team has developed a potentially safer way to monitor drug delivery to the brain.

Mapping drugs in the brain and assessing how well they reach it are both vitally important for testing new pharmaceuticals for brain diseases. But until now, this could be done only by using radioactive chemicals, which are expensive and risk human safety.

In their search for a lower risk alternative, Rumiana Bakalova of the National Institute of Radiological Sciences in Chiba, Japan, and colleagues in Japan and Bulgaria have developed a non-radioactive way to monitor conventional drugs in the brain. By attaching nitroxyl radicals to the anticancer drug lomustine they found that its movement into the brain could be tracked using magnetic resonance imaging.

Adding the nitroxyl radicals does not affect the drug's movement through the blood–brain barrier, which is a crucial step for the drug, explains Bakalova. 'We observed that the drug was localised in the brain tissue and were able to map the drug localisation in different parts of the brain,' she says. This information could be useful for planning chemo- and radiotherapy of cancer and other diseases, she adds.



Adding a nitroxyl radical to lomustine allows the drug to be mapped in the brain

Baklova's team now plans to look into using the labelling for other dugs and also to map drugs in different organs and tissues in the body.

Sarah Dixon

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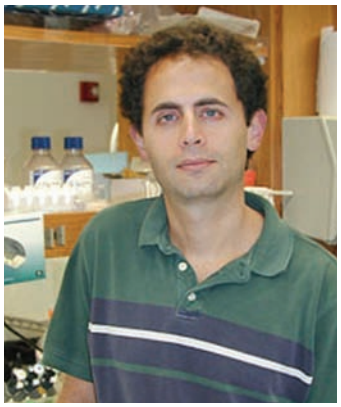
Interview

Shining a light on the proteome

Ben Cravatt talks to Michael Smith about his research into the function of the proteome and success in cloning the cDNA of a hotly pursued enzyme



Ben Cravatt

Benjamin Cravatt is a professor and chair of the Department of Chemical Physiology at The Scripps Research Institute in California, US. His research combines synthetic organic chemistry, proteomics and metabolomics. He is a member of the *Molecular BioSystems* editorial board.

What inspired you to become a scientist?
There wasn't a plan from birth, but my Dad, a dentist, and my Mom, a dental hygienist, inspired me to think about biology. I went to Stanford University in the US with a view to going to medical school. My major subject was biology and I got the chance to work in John Griffin's bio-organic chemistry lab. That inspired me not only to do research, but also to work at the interface of the chemical and biological disciplines.

How did you decide what to do at graduate school?
Most graduate programmes in the early nineties were very restrictive. You were expected to see yourself as a chemist or a biologist and encouraged to pursue a sub-discipline in one of these subjects. However, the Scripps Institute in California aimed to keep their students as dedifferentiated as possible. Students were allowed to use whatever technologies they wanted to address problems at the interface of medicine and molecular sciences. I started at Scripps and never looked back!

What did you do after your PhD?
I'd been fortunate in graduate school to succeed in purifying and cloning the enzyme fatty acid amide hydrolase (FAAH) and cloning its cDNA. FAAH degrades endogenous lipids in our nervous system involved in interacting with the cannabinoid receptor. It was a hotly pursued enzyme by several labs and we just happened to use chemical approaches to enrich it using synthetic inhibitor columns. This gave us the opportunity to dive into that field with a unique set of tools. At that time, the Skaggs Institute for Chemical Biology started at Scripps was keen to bring in young people and I got the opportunity to join the faculty.

What kind of research do you do?
We range from using synthetic organic chemistry, proteomics and metabolomics to mouse genetics and animal pharmacology. We use chemical and systems biology techniques to shine a light on the 50 per cent or so of the proteome that is still uncharacterised to discover and understand its function. That means going from the biochemical characterisation of an enzyme to identifying its endogenous substrates and products, the pathways those exist in and the ramifications of perturbing those pathways in higher organisms. This usually gets us into mouse genetics and pharmacology at some point.

What aspects of mammalian biology are you interested in?
We're interested in enzymes that regulate small molecule metabolism and signalling pathways. Such enzymes are a rich source of interesting new biology and potential therapeutics. If you look at the number of enzymes for which there are drugs on the market today, more than 70 per cent perform chemistry on small molecules.

Metabolic pathways that regulate similar molecules in mammals tend to be in pathways controlling higher-order behavioural/physiological functions and their perturbation can produce effects on processes ranging from inflammation to cognition and depression. Monoamine oxidase and COX inhibitors are excellent examples of drugs that perturb enzymes that regulate small molecule signals. I think that's a great area for chemical biologists to exploit because you have enzymes that are druggable and the pathways they regulate are essentially organic chemistry.

How do you think this field is going to develop?
We've gotten to this stage thanks to the successes in genome sequencing. The challenge from now on is to understand how all these identified proteins function in the cell and to identify promising therapeutic targets.

It's hard to say that the proteome will ever be fully understood. In 20 years we'll have a much better appreciation of primary binding partners – substrates of enzymes – but how it all fits together in the cell is a lot to work on. Large-scale mass spectrometry is still slow. The high spatial distribution and temporal resolution needed is still in development and how it translates into what is going on in the cell is a big challenge.

If you weren't a scientist, what would you be?
I don't think any other job would inspire me as much. There's freshness and a drive when working with talented colleagues in an environment that is always changing. However, I was a competitive athlete at college, which I miss, so if I wasn't a scientist, maybe I'd dream of being a professional athlete.

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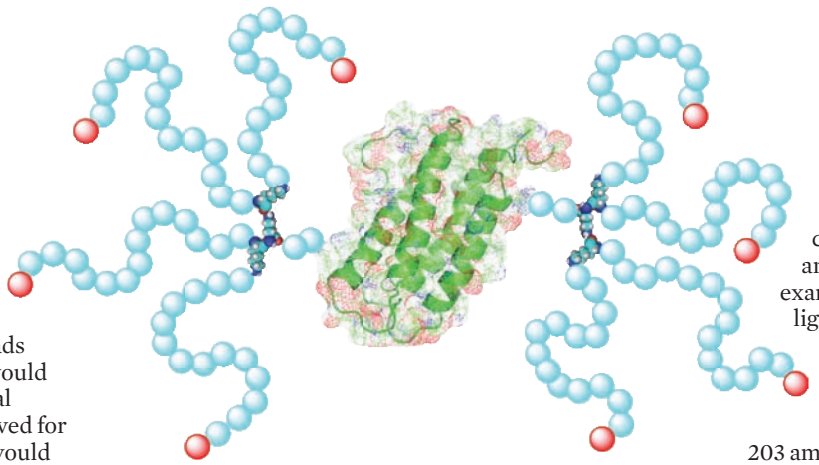
Instant insight

Chemical connections

Building a protein can be likened to a jigsaw puzzle. Stephen Kent of the University of Chicago, US, puts the pieces together



Chemical ligation was used to create an active analogue of erythropoietin – a protein that stimulates red blood cell production

A long-held goal of protein science has been to apply chemistry's tools to understand how a protein's structure leads to its function. Ideally this would be achieved by total chemical synthesis which, once achieved for a particular protein target, would give complete control over the protein's covalent structure. Simply modifying the synthesis would allow a chemist to incorporate site-specific labels and create a wide variety of novel chemical analogues.

However, until recently, proteins have resisted total chemical synthesis because of their large size. The smallest proteins have about 50 amino acid residues in their polypeptide chain, while proteins of typical size have in the region of 300. Yet chemical peptide synthesis cannot routinely make molecules containing more than around 40 to 50 amino acid residues. This was the conundrum that – until the mid-1990s – confronted the researcher who wished to apply the full power of chemical science to study proteins.

Now, all that has changed. In the early 1990s, a new principle was proposed: chemoselective condensation of unprotected peptide segments. This has led to the efficient total chemical synthesis of proteins. In a chemoselective condensation reaction, two unique, mutually reactive chemical functional groups are employed, one on each of the reacting peptide segments. These groups are designed to react with one another, but to NOT react with any of the other functional groups found in protein-derived peptides. When these two peptide segments are mixed in solution, an unambiguous reaction ensues to form a single product in essentially quantitative yield. The process is called chemical ligation.

The chemical ligation principle surmounts the difficulties that limited traditional solution and solid phase synthetic approaches. Use of unprotected peptide building blocks means that the starting materials, intermediate products, and the final full length synthetic polypeptide chain can all be purified by standard methods, and characterised by high resolution techniques such as reverse phase HPLC and electrospray mass spectrometry. Reactions can be carried out at high concentrations, since the lack of protecting groups means the peptides are freely soluble in solvents such as aqueous 6M guanidine·HCl. Consequently, reactions are rapid and go to completion. The full length synthetic polypeptide chains fold with high efficiency to give the tertiary structure, including disulfide bonds, of the functional protein molecule.

Chemical ligation has enabled a wide variety of proteins to be prepared efficiently, some containing 200 or more amino acid residues. For example, native chemical ligation, which links a protein segment containing a thioester to one with an N-terminal cysteine residue, was used to make a 203 amino acid residue form of the HIV-1 protease enzyme, with full catalytic activity. The technique has also been used to create an analogue of erythropoietin (see figure), a protein that stimulates red blood cell production. The glycoprotein mimetic had a mass of over 50 kiloDaltons and showed enhanced properties including a ~3-fold extended lifetime in vivo.

In a tribute to George W Kenner and colleagues, who thirty years ago attempted the total synthesis of the enzyme consensus lysozyme by conventional solution methods, chemical ligation has led to a fully convergent chemical synthesis of human lysozyme. Four unprotected peptide segments were connected to give a 130 amino acid polypeptide chain that was folded to give a protein with four disulfide bridges. The crystalline synthetic enzyme had full activity.

An elegant and practical solution to the grand challenge of protein synthesis, chemical ligation offers a way to make designer proteins with novel, and improved, properties. It also enables the science of chemistry to be applied, without limitation, towards unravelling the molecular basis of protein function.

Read more in Stephen Kent's tutorial review 'Total chemical synthesis of proteins' in Chemical Society Reviews.

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Essential elements

Journal celebrations

The new year brings a host of celebrations for RSC journals. *Soft Matter* and *Molecular BioSystems* mark their fifth year of publication in 2009 and look back over a catalogue of successes. Since their launch in 2004, both journals have gone from strength to strength, establishing themselves as leading publications in their field. At 4.12,* the latest impact factor for *Molecular BioSystems* is a sure indication of the significance of the work in this exciting interdisciplinary journal, publishing cutting-edge research at the interface between the -omic sciences and systems biology. *Soft Matter* – as the number one journal in the field for both impact and immediacy – is first choice for fundamental soft matter research.

For *Soft Matter,* 2009 marks a double celebration as – thanks to a continued increase in submissions – the journal moves from publishing 12 to 24 issues a year. What better measure of the journal's success? In fact, 2008 saw journal submissions and acceptances across the whole of RSC Publishing increase by 33% and 29%, respectively. Joining *Soft Matter* in reflecting this achievement, the frequency of two other journals is set to double in 2009. Leading journal in miniaturisation science, *Lab on a Chip*, also moves to 24 issues: an indication of the significant increase in submissions over the years. Hardly surprising: with an impact factor of 5.1* *Lab on a Chip* guarantees high visibility and quality research. Review journal *Natural Product Reports* (*NPR*), with an impact factor of 7.67*, doubles to 12 issues, meaning you can now get hold of the most topical reviews in key areas even faster, including bioorganic chemistry, chemical biology, natural product synthesis, chemical ecology and carbohydrates.

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23 years of devotion

When Jim Harnley joined the *Journal of Analytical Atomic Spectrometry* (*JAAS*) as the North American Editor in 1985, little did he expect to become the longest serving member of the *JAAS* staff and editorial board.

After 23 years of service with *JAAS*, Jim is now retiring from his position but will maintain his association with the journal as a member of the advisory board.

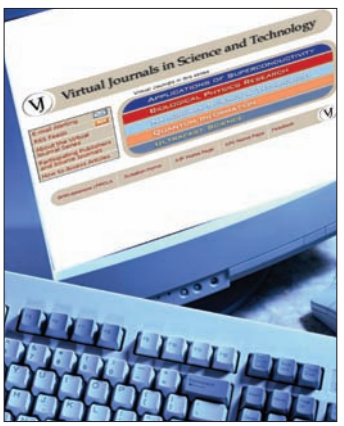
He reminisces on his early days: 'My position was established in an attempt to shorten the manuscript review time. At that time, prior to e-mail, correspondence between

the US and the UK took a week (unless you forgot to put air mail on the envelope, in which case delivery sometimes took two months). Submission and review in the US could shorten the process by up to two weeks.'

'Jim has been involved with *JAAS* since the launch of the journal and has contributed significantly to its continuing success. As editor for the Americas, he has been very successful at raising and maintaining the profile of the journal in this region and we would like to thank him for all his hard work,' says Niamh O'Connor, *JAAS* editor. In 2009 *JAAS* marks its 24th year of publishing innovative research on the fundamental theory, practice and analytical application of spectrometric techniques to elemental research.

Virtual collaboration

Articles from selected RSC Journals are now included in the Virtual Journals in Science and Technology series, sponsored by the American Institute of Physics and the American Physical Society. Each of the virtual journals presents an online collection of relevant papers from a broad range of 'source' journals in the physical sciences selected by expert editors.



'We're very pleased that the RSC is contributing to the Virtual Journals, and we're certain that the addition of their publications will make it easier for specialists in the fields covered by the series to stay current with the top-flight research published by the Society,' says Mark Cassar, AIP publisher, Journals and Technical Publications.

Browse the virtual journals at www.virtualjournals.org

Chemical Biology (ISSN: 1747-1605) is published monthly by the Royal Society of Chemistry, Thomas Graham House, Science Park, Milton Road, Cambridge UK CB4 0WF. It is distributed free with *Chemical Communications*, *Organic & Biomolecular Chemistry*, *Lab on a Chip*, *Integrative Biology*, *Metallomics*, *Molecular BioSystems*, *Natural Product Reports*, *Dalton Transactions* and *Photochemical & Photobiological Sciences*. *Chemical Biology* can also be purchased separately. 2009 annual subscription rate: £199; US $396. All orders accompanied by payment should be sent to Sales and Customer Services, RSC (address above). Tel +44 (0) 1223 432360, Fax +44 (0) 1223 426017. Email: sales@rsc.org

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