

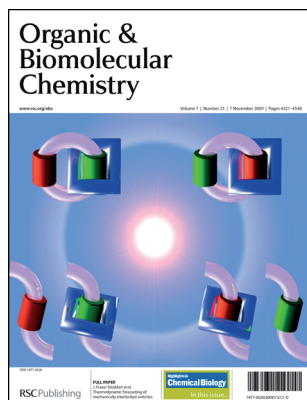
Organic & Biomolecular Chemistry

An international journal of synthetic, physical and biomolecular organic chemistry
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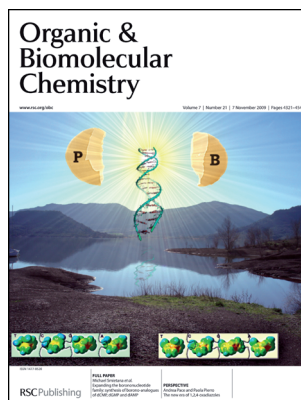
ISSN 1477-0520 CODEN OBCRAK 7(21) 4321–4548 (2009)



Cover

See J. Fraser Stoddart *et al.*, pp. 4391–4405.
The effects of structural modifications on the difference in free energy (ΔG°) for the equilibrium processes in switchable mechanically interlocked molecules can be predicted by considering, firstly, the interactions present in their precursor pseudorotaxanes. Artwork by Mark A. Olson.

Image reproduced by permission of Mark A. Olson from *Org. Biomol. Chem.*, 2009, **7**, 4391.



Inside cover

See Michael Smietana *et al.*, pp. 4369–4377.
Inspired by Salvador Dali's painting "jaune d'oeuf soleil" this artwork, representing the Salagou Lake near Montpellier, asks the question whether boron might have played a role in the pre-RNA world. We describe here the synthesis of the four 2'-deoxyboronucleotide analogues of natural nucleotide monophosphates and demonstrate that these analogues form a new borono-based internucleosidic linkage with uridine.

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HIGHLIGHTS IN CHEMICAL BIOLOGY

B81

Highlights in Chemical Biology provides a 'snapshot' of the latest developments in chemical biology from all RSC publications, showcasing newsworthy articles and significant scientific advances.

Highlights in Chemical Biology

November 2009/Volume 4/Issue 11

www.rsc.org/highlightschembiol

PERSPECTIVE

4337

The new era of 1,2,4-oxadiazoles

Andrea Pace* and Paola Pierro

This survey includes historical background, general features and state-of-the-art applications about the synthesis, the chemical and photochemical reactivity, and the use of 1,2,4-oxadiazoles in materials and as bioactive compounds.



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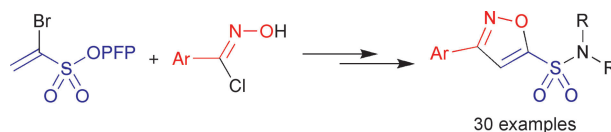
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4349

3,5-Isoxazoles from α -bromo-pentafluorophenyl vinylsulfonates: Synthesis of sulfonates and sulfonamides

Chieh Chien Lee, Richard J. Fitzmaurice and Stephen Caddick*

The efficient synthesis of isoxazole sulfonates and sulfonamides has been achieved *via* a 1,3-dipolar cycloaddition/aminolysis sequence on the key α -bromo-pentafluorophenyl vinylsulfonate building block.

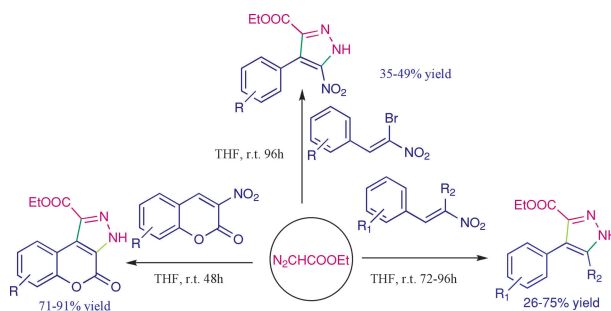


4352

Efficient method for the synthesis of functionalized pyrazoles by catalyst-free one-pot tandem reaction of nitroalkenes with ethyl diazoacetate

Jian-Wu Xie,* Zheng Wang, Wei-Jun Yang, Li-Chun Kong and Dong-Cheng Xu

An efficient method for the synthesis of functionalized pyrazoles by catalyst-free one-pot tandem reaction of nitroalkenes with ethyl diazoacetate has been investigated.

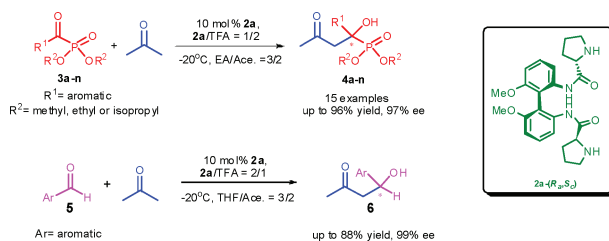


4355

Chiral biphenylamide derivative: an efficient organocatalyst for the enantioselective synthesis of α -hydroxy phosphonates

Jun Jiang, Xiaohong Chen, Jun Wang, Yonghai Hui, Xiaohua Liu, Lili Lin and Xiaoming Feng*

The aldol reactions of α -keto phosphonates and aldehydes were facilitated by an axially chiral biphenylprolinamide under mild conditions, affording the synthetically and pharmaceutically useful products in high yields and excellent enantioselectivities.

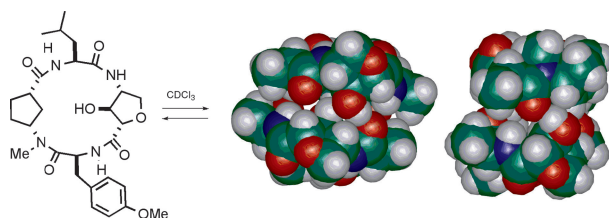


4358

α,γ -Cyclic peptide ensembles with a hydroxylated cavity

César Reiriz, Manuel Amorín, Rebeca García-Fandiño, Luis Castedo and Juan R. Granja*

Here we describe a self-assembling α,γ -cyclic tetrapeptide that contains the 4-amino-3-hydroxytetrahydrofuran-2-carboxylic acid, in which the hydroxy group is pointing towards the inner cavity of the resulting dimers.



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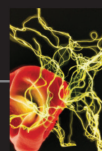
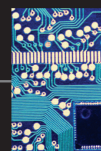
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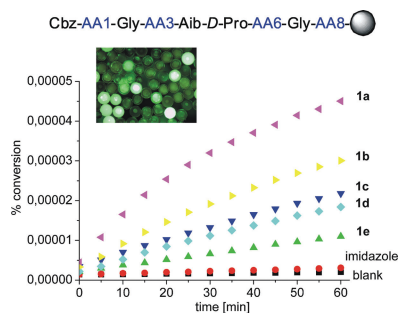


4362

Hydrolytic activity of histidine-containing octapeptides in water identified by quantitative screening of a combinatorial library

Carsten Schmuck,* Ute Michels and Jürgen Dudaczek

A quantitative on-bead screening of a combinatorial octapeptide library revealed catalysts with hydrolytic activity in water. Histidine is an essential amino acid but the catalytic activity as well as the substrate binding affinity is also dependent on the sequence of the octapeptide.

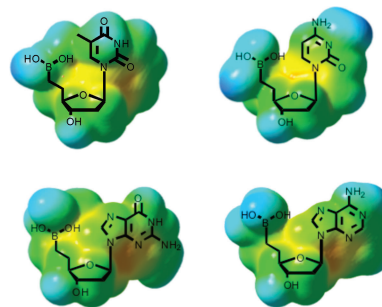


4369

Expanding the boronucleotide family: synthesis of borono-analogues of dCMP, dGMP and dAMP

Anthony R. Martin, Kishor Mohanan, Delphine Luvino, Nicolas Floquet, Carine Baraguey, Michael Smietana* and Jean-Jacques Vasseur*

We report here the synthesis of nucleotide analogues of the natural dTMP, dCMP, dGMP and dAMP in which the 5'-phosphate has been replaced by a boronic acid function. We have also studied by ^1H NMR the complexation with uridine of these previously unknown compounds.

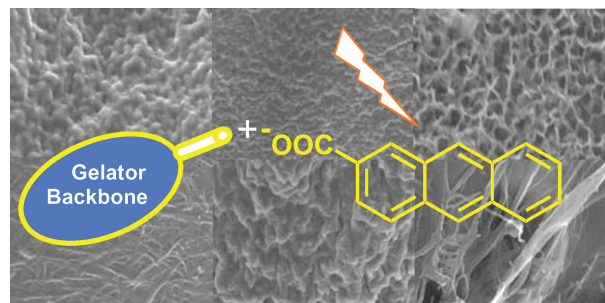


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Studies on a new class of organogelator containing 2-anthracenecarboxylic acid: Influence of gelator and solvent on stereochemistry of the photodimers

Arnab Dawn, Norifumi Fujita,* Shuichi Haraguchi, Kazuki Sada, Shun-ichi Tamaru and Seiji Shinkai*

The stereochemistry of the photodimers obtained from 2-anthracenecarboxylic acid containing organogelators can be controlled by the solvent polarity and the gelator structure; also, the photochemical process has a pronounced influence on the gel structure.

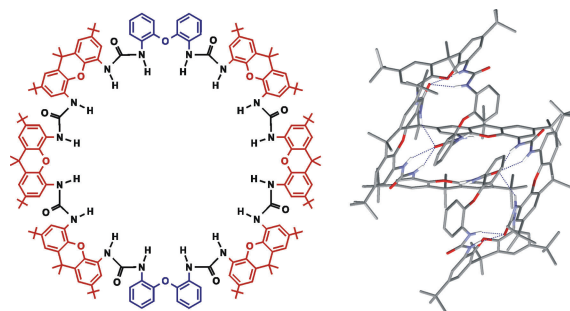


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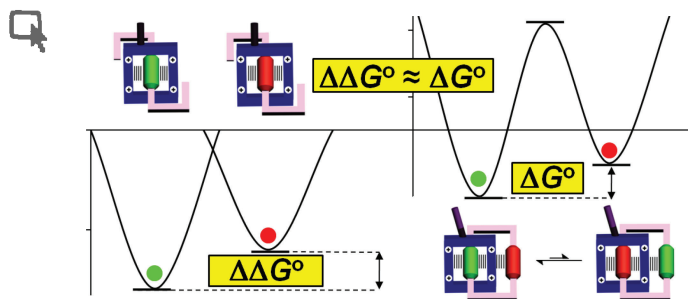
Macrocyclic oligoureas with xanthene and diphenyl ether units

Denys Meshcheryakov, Michael Bolte and Volker Böhmer*

As potential anion receptors, cyclic oligoureas with 64- and 80-membered rings in which two sets of three or four rigid xanthene (X) units are connected *via* flexible diphenyl ether (D) units have been synthesized and characterized by ^1H NMR. Single crystal X-ray diffraction and interaction with anions followed by ^1H NMR give deeper insights into the binding and conformation of the octamer.



4391

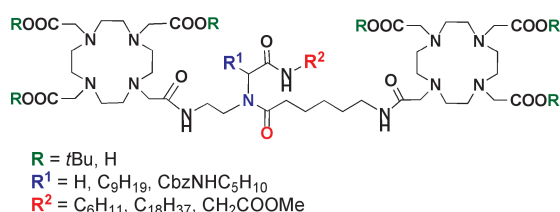


Thermodynamic forecasting of mechanically interlocked switches

Mark A. Olson, Adam B. Braunschweig, Taichi Ikeda, Lei Fang, Ali Trabolsi, Alexandra M. Z. Slawin, Saeed I. Khan and J. Fraser Stoddart*

A Thermodynamic Forecast for the Mechanical Bond! The changes ($\Delta\Delta G^\circ$ values) in the difference of free energy during the formation of different pseudorotaxanes can subsequently be extrapolated to predict ΔG° values for the thermodynamics associated with switching in analogous MIM switches, employing the same donor–acceptor recognition components.

4406

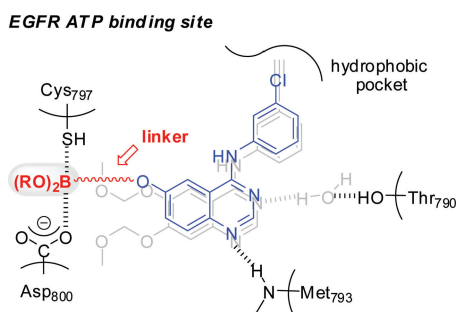


Application of the Ugi four-component reaction to the synthesis of ditopic bifunctional chelating agents

Lorenzo Tei, Giuseppe Gugliotta, Stefano Avedano, Giovanni B. Giovenzana and Mauro Botta*

The Ugi four-component reaction is used for the first time to obtain a variety of bifunctional ditopic Gd-complexes starting from DOTA monoamide derivatives as amino and acid components.

4415

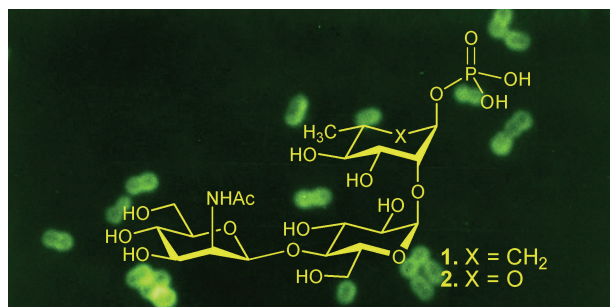


Discovery of boron-conjugated 4-anilinoquinazoline as a prolonged inhibitor of EGFR tyrosine kinase

Hyun Seung Ban, Taikou Usui, Wataru Nabeyama, Hidetoshi Morita, Kaori Fukuzawa and Hiroyuki Nakamura*

We have designed and synthesized boron-conjugated quinazoles as prolonged inhibitor of EGFR, providing a new insight into the biological properties of boron.

4428



Synthesis, molecular dynamics simulations, and biology of a carba-analogue of the trisaccharide repeating unit of *Streptococcus pneumoniae* 19F capsular polysaccharide

Laura Legnani, Silvia Ronchi, Silvia Fallarini, Grazia Lombardi, Federica Campo, Luigi Panza, Luigi Lay, Laura Poletti, Lucio Toma, Fiamma Ronchetti and Federica Compostella*

The synthesis of carba-analogue **1** is herein presented. Conformational and biological studies show that compound **1** is a good mimic of the natural trisaccharide repeating unit **2**.

2010 Meetings (in chronological order)

NF- κ B in Inflammation & Disease
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Structural Genomics: Expanding the Horizons of Structural Biology
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Advances in Molecular Mechanisms of Atherosclerosis
The Macrophage: Intersection of Pathogenic & Protective Inflammation
Antibiotics & Resistance: Challenges & Solutions (new!)

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Cell Biology of Virus Entry, Replication & Pathogenesis
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Metabolism & Cancer Progression (new!)

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Viral Immunity
Nuclear Receptors: Signaling, Gene Regulation & Cancer
Nuclear Receptors: Development, Physiology & Disease
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Integration of Developmental Signaling Pathways
G Protein-Coupled Receptors
Dynamics of Eukaryotic Transcription During Development
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Towards Defining the Pathophysiology of Autistic Behavior
Malaria: New Approaches to Understanding Host-Parasite Interactions
Molecular Targets for Control of Vector-Borne Diseases: Bridging Lab & Field Research*
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The Prous Institute-Overton and Meyer Award for New Technologies in Drug Discovery

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The nominations should be submitted to the Chairman of the Juries, Professor Gerhard Ecker, President of EFMC, Department of Medicinal Chemistry, University of Vienna, Althanstrasse 14, A-1090 Wien, Austria Fax: +43-1-4277-9551 E-mail: awards@efmc.info

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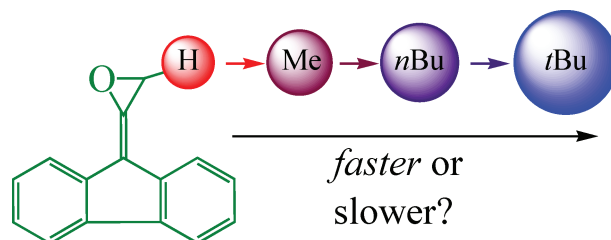
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Effect of steric bulk on the absolute reactivity of allene oxides

Mark W. Konecny and Norman P. Schepp*

Increasing the steric bulk of alkyl groups at the epoxide carbon of substituted fluorenylidene allene oxides affects reactivity in a manner opposite to that normally observed for other allene oxides.

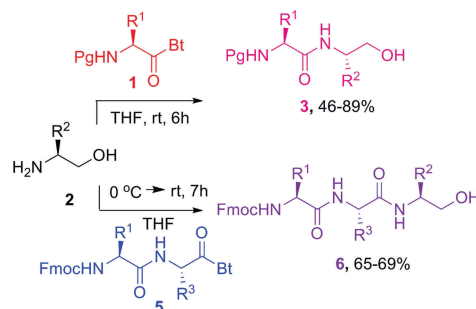


4444

An efficient method for the preparation of peptide alcohols

Alan Roy Katritzky,* Nader Elmaghwy Abo-Dya, Srinivasa Rao Tala, Kapil Gyanda and Zakaria Kamel Abdel-Samii

N-Protected dipeptide alcohols (**3**) and tripeptide alcohols (**6**) were synthesized by treatment of various amino alcohols with *N*-protected(α -aminoacyl)benzotriazoles (**1**) and *N*-protected(α -dipeptidoyl)benzotriazoles (**5**) respectively in good yields with complete retention of chirality.

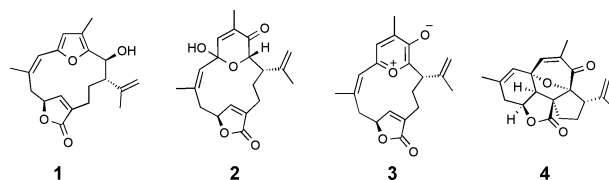


4448

Total synthesis of (+)-intricarene using a biogenetically patterned pathway from (–)-bipinnatin J, involving a novel transannular [5+2] (1,3-dipolar) cycloaddition

Bencan Tang, Christopher D. Bray and Gerald Pattenden*

Oxidative cleavage of the furan ring in **1** leads to the hydroxypyranone **2**, which was converted by acetylation and heating into the butenolide-oxidopyrylium ion **3**, which gave intricarene **4** via transannular [5+2] (1,3-dipolar) cycloaddition.

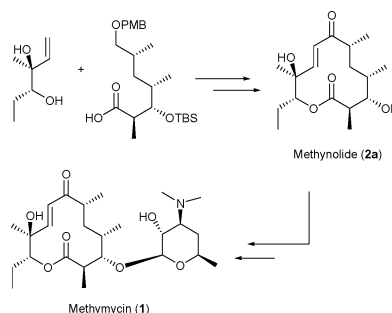


4458

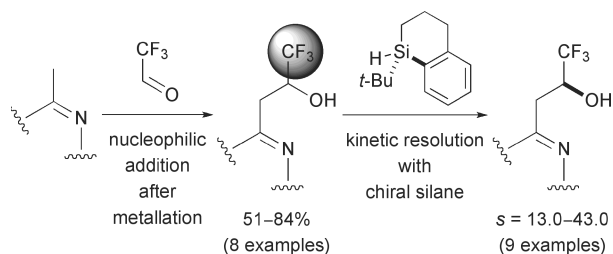
Total synthesis of methymycin

Hong-Se Oh, Richeng Xuan and Han-Young Kang*

The total synthesis of methymycin was achieved by coupling of the trichloroimidate derivative of D-desosamine and methynolide, which was prepared by ring-closing metathesis as the key reaction.



4464

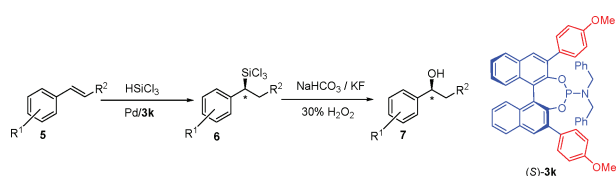


Facile preparation of CF_3 -substituted carbinols with an azine donor and subsequent kinetic resolution through stereoselective Si–O coupling

Anne Steves and Martin Oestreich*

Enantiomerically enriched, α - CF_3 -substituted carbinols containing an azine donor are prepared from fluoral followed by reagent-controlled Si–O coupling.

4470

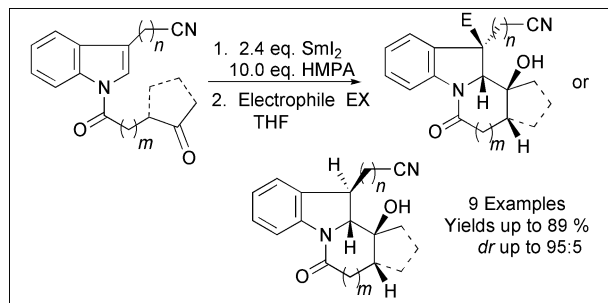


Synthesis and application of bulky phosphoramidites: highly effective monophosphorus ligands for asymmetric hydrosilylation of styrenes

Feng Zhang and Qing-Hua Fan*

New bulky binaphthol based phosphoramidite ligands were prepared and successfully applied in the Pd-catalyzed asymmetric hydrosilylation of styrenes with high enantioselectivities, and excellent catalytic activities and productivities.

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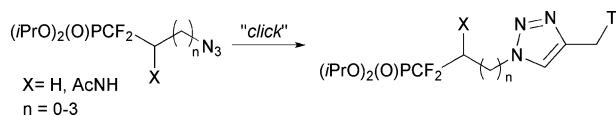


Highly diastereoselective samarium diiodide induced cyclizations of new 3-substituted indole derivatives

Christine Beemelmans and Hans-Ulrich Reissig*

Starting from new N-acyl indole derivatives, we obtained highly functionalized tricyclic and tetracyclic indole derivatives in moderate to very good yields and with excellent diastereoselectivities. Further transformations to synthetically useful intermediates were also possible.

4481



Synthesis of fluorophosphonylated acyclic nucleotide analogues via copper(I)-catalyzed Huisgen 1-3 dipolar cycloaddition

Sonia Amel Diab, Antje Hienzsch, Cyril Lebargy, Stéphane Guillaume, Emmanuel Pfund and Thierry Lequeux*

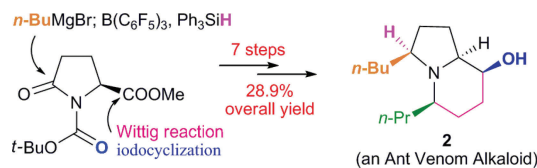
The syntheses of fluorophosphonylated purine and pyrimidine derivatives are reported as new and rapid access to potential nucleoside phosphorylase inhibitors.

4491

A concise and fully selective synthesis of the ant venom alkaloid (3*S*,5*R*,8*S*,9*S*)-3-butyl-5-propyl-8-hydroxyindolizidine

Geng-Jie Lin and Pei-Qiang Huang*

An enantioselective synthesis of the indolizidine alkaloid (**2**) was achieved in seven steps with an overall yield of 28.9%. All the reaction steps proceeded with excellent chemo-, regio- and/or diastereoselectivities.



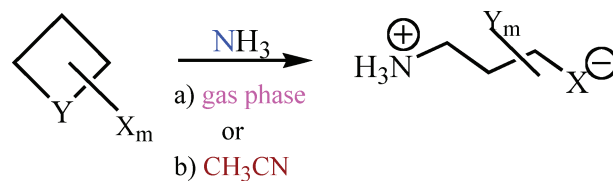
key step: iodocyclization of allylic urethane **8**
key feature: highly chemo-, regio-, and/or diastereo-selective for all steps

4496

Is nucleophilic cleavage chemistry practical for 4-membered heterocycles?

Harold D. Banks*

The rates of cleavage of azetidines, oxetanes and thietanes by ammonia can be dramatically increased by halogen substitution as determined by *ab initio* calculations in the gas phase and in acetonitrile solution. The importance of potentially competitive halide displacement reactions was assessed to establish the overall reaction outcomes.



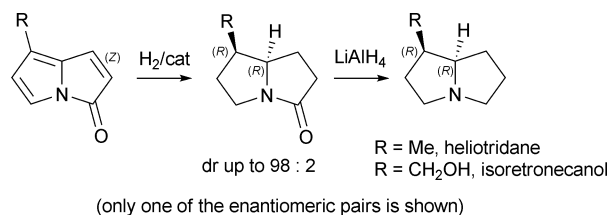
Y = NH, O, S; X = F, Cl, Br; m = 0 - 2.

4502

Hydrogenation of pyrrolizin-3-ones; new routes to pyrrolizidines

Xavier L. M. Despinoy and Hamish McNab*

Pyrrolizin-3-ones can be easily hydrogenated to their hexahydro (pyrrolizidin-3-one) derivatives in the presence of heterogeneous catalysts. Good diastereoselectivity can be achieved if the pyrrolizin-3-one is substituted at the 1- (or 7-) position(s), but the selectivity is reduced if both positions are substituted. Subsequent deoxygenation of the pyrrolizidin-3-ones provides concise, diastereoselective routes to necine bases.

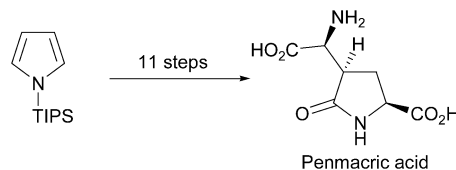


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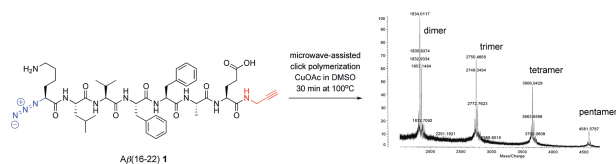
From *N*-triisopropylsilylpyrrole to an optically active C-4 substituted pyroglutamic acid: total synthesis of penmacric acid

Christophe Berini, Nadia Pelloux-Léon,*
Frédéric Minassian* and Jean-Noël Denis

The stereoselective synthesis of penmacric acid, an optically active C-4 substituted pyroglutamic acid, has been efficiently achieved through an unusual 11-step sequence starting from simple *N*-triisopropylsilylpyrrole.



4517

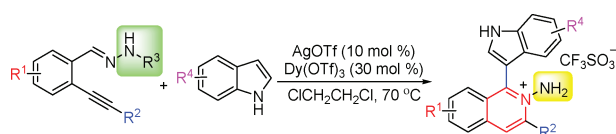


Microwave-assisted click polymerization for the synthesis of Aβ(16–22) cyclic oligomers and their self-assembly into polymorphous aggregates

Ronald C. Elgersma, Maarten van Dijk, Annemarie C. Dechesne, Cornelus F. van Nostrum, Wim E. Hennink, Dirk T. S. Rijkers and Rob M. J. Liskamp*

The design, synthesis, and structural analysis of cyclic oligomers with an amyloidogenic peptide, the Alzheimer Aβ(16–22) sequence, as the repeating unit to obtain novel self-assembling bionanomaterials are described.

4526

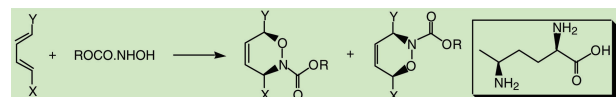


Multicatalytic tandem reaction of *N'*-(2-alkynylbenzylidene)hydrazide with indole

Xingxin Yu, Xiaodi Yang and Jie Wu*

The combination of AgOTf and Dy(OTf)₃ shows high efficiency as a catalyst in the tandem reactions of *N'*-(2-alkynylbenzylidene)hydrazides with indoles, which generate the unexpected 1-(indol-3-yl)-2-aminoquinolinium triflates in good yields.

4531

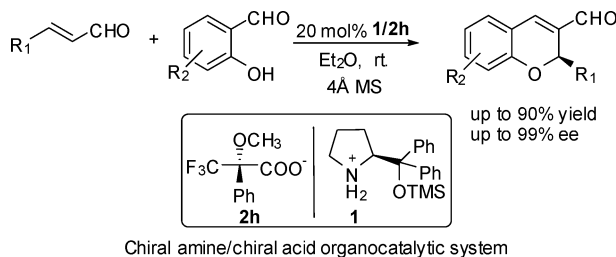


The acyl nitroso Diels–Alder (ANDA) reaction of sorbate derivatives: an X-ray and ¹⁵N NMR study with an application to amino-acid synthesis

Lee Bollans, John Bacsá, Jonathan A. Iggo, Gareth A. Morris and Andrew V. Stachulski*

We discuss structure–reactivity trends, especially regioisomer ratios, in the acyl nitroso Diels–Alder reactions of sorbate ester and sorbic alcohol derivatives. We describe an efficient synthesis of 5-methyl ornithine and present X-ray crystal structure data and a novel ¹⁵N NMR method for assignment of the regioisomers.

4539



Chiral amine/chiral acid as an excellent organocatalytic system for the enantioselective tandem oxa-Michael-aldol reaction

Shu-Ping Luo, Zhao-Bo Li, Li-Ping Wang, Yi Guo, Ai-Bao Xia and Dan-Qian Xu*

The chiral amine/chiral acid organocatalytic system of (*S*)-diphenylpyrrolinol trimethylsilyl ether with the (*S*)-Mosher acid showed an excellent synergistic effect and efficient steric effect in the tandem oxa-Michael-aldol reaction.

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Highlights in Chemical Biology

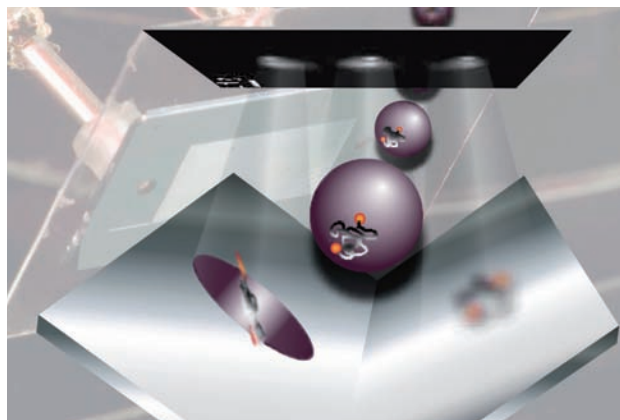
Reflecting chip allows fast 3D DNA observation

Scrutinising cells with mirrors

A chip that can be used to track biological processes in three dimensions inside living cells has been developed in France.

Aurélien Bancaud and co-workers from the University of Toulouse, made the device, which uses microscale V-shaped mirrors to provide simultaneous views of biological specimens from different vantage points. This allows the team to use a regular upright microscope to follow cell processes in 3D on a fast timescale.

'Modern live cell imaging calls for new methods that achieve fast and minimally invasive 3D observation,' explains Bancaud. Current methods can involve acquiring several views of the same specimen, meaning high doses of illumination are needed – which can be detrimental to the cells. The multiple observation process is also slower, so fast events cannot be easily tracked. Pyramidal mirrors have been proposed for multiple vantage point imaging and 3D tracking in vitro, but these



systems were not integrated in a lab-on-a-chip device, limiting their applicability for live cell imaging, says Bancaud.

Bancaud's group made the device using micromachining technology to form metal coated trenches in a silicon wafer. The metal coating acts as a mirror and particles such as cells can be introduced into the V-shaped trenches. The researchers

incorporated their device into a standard fluorescence microscope and loaded the wafer with yeast cells modified to express a fluorescent protein. The group was able to use the device to follow the fluorescent protein and so study fast DNA movements in chromosomes within the cell nuclei.

Enrico Gratton, an expert in fluorescence microscopy for imaging live cells from the University of California, Irvine, US, says the lab-on-chip device is 'a very clever use of microfabrication. The advantage of the method is that it only requires a normal wide field microscope and the chip,' he adds.

Bancaud suggests that in future the technology might be useful for observing processes in cells from different biological systems where fast tracking is necessary. He adds that it might be tempting to try adding temperature sensors or actuators to this type of device, to further control the cell environment. *Fay Nolan-Neylan*

Bancaud's mirrored chip can be used to study chromatin dynamics inside cells

Reference
H Hajjoul *et al*, *Lab Chip*, 2009, DOI: 10.1039/b909016a

In this issue

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Cutting and pasting with the human genome

DNA scissors cut human genomic DNA at one target site

Evolving evolution

In this month's interview, Frances Arnold discusses why nature's designs work the way they do

Instant insight: Making synthetic cells

Cell and organelle mimics typically perform one simple function. But what about more complicated systems?

Instant insight: Triple therapy to target tumours

Why good things come in threes when it comes to cancer therapy



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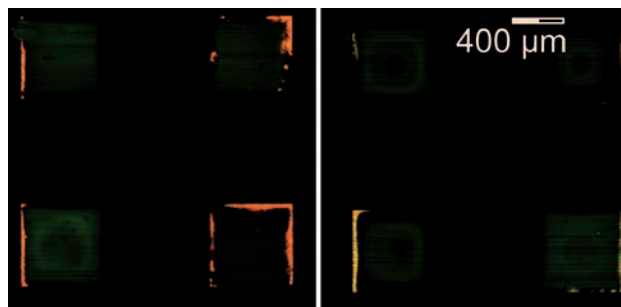
Research highlights

Combined technologies distinguish cells differing by one DNA base mutation

Screening genes from clones – fast

A high throughput genetic screening method developed by Swedish scientists could eventually lead to personalised medical treatment for genetic diseases, they claim. The method takes single cells and grows them in colonies before analysing their DNA.

The Swedish team, led by Helene Andersson-Svahn at the Royal Institute of Technology, Stockholm, combined several established technologies into an integrated system. Clones are grown in parallel from single cells held in microscale wells within a chip. The cells are then broken open to release their DNA and a polymerase chain reaction (PCR) is used to multiply the amount of DNA. This double stranded DNA is then captured onto magnetic beads and denatured to form single stranded DNA. Finally, a reporter molecule that fluoresces when it binds a particular DNA sequence is added, allowing mutations or differences



Fluorescent reporters spot the difference between the DNA of two cell lines in microwells

between samples to be spotted. The researchers were able to use the system to distinguish cells from two human cell lines differing by one base mutation in their DNA.

The integrated system means that all the steps can be carried out on the one chip – for example, a magnetic field can be applied to keep the magnetic beads and DNA in the wells while the surrounding medium is changed. The result is the ‘first study that links clonal expansion with PCR and genetic sequencing in one system,’ says Andersson-Svahn.

Reference
S Lindström *et al*, *Lab Chip*, 2009, DOI: 10.1039/b912596e

Ulf Landegren, an expert in molecular medicine at Uppsala University, Sweden, explains why analysing cell colonies derived from a single cell is important. ‘It is becoming increasingly clear that analyses of cells in bulk may miss important factors like the division of labour among cells in a tissue and variation among cells according to state of development, cell cycle phase and influence by external factors,’ he says. This is behind the ‘rapidly increasing interest in single cell analyses to study the molecular properties of individual cells,’ he adds.

Andersson-Svahn says that the ultimate aim of developing the technology is to allow fast, high throughput and low cost genetic screening. Such screening would be an important step for developing personalised treatment for genetic diseases and some types of cancer, she adds.

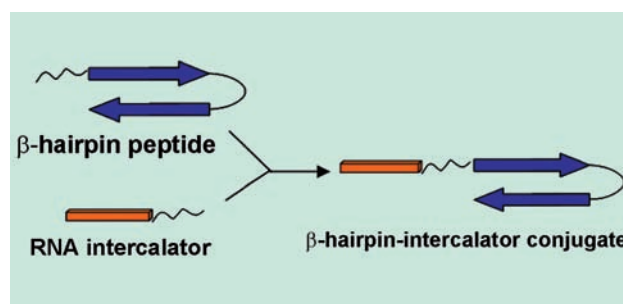
Russell Johnson

Linking ligands gives RNA binder far better than the sum of its parts

Two-pronged approach to RNA binding

The prospect of using RNA as a drug target is of great interest to scientists, but due to its complex structure, designing ligands that bind to it is challenging. Scientists from the University of North Carolina at Chapel Hill, US, have overcome these difficulties by combining two weak ligands to make an RNA-binding conjugate that is far better than the sum of its parts.

‘Although cooperative binding has been explored in the past,’ says Marcey Waters, who carried out the research with Lauren Cline, ‘our system is the first example of coupling a sequence-selective threading intercalator with a β -hairpin peptide that is known to selectively bind unpaired bases.’ The result is a system that simultaneously targets both the single- and double-stranded regions of RNA. While the



Combining two RNA-binding ligands gives a conjugate that binds both single and double stranded regions of RNA

intercalator threads between two G–C base pairs adjacent to bulges in the RNA, the peptide targets exposed bases in the RNA’s single-stranded loops and bulges, resulting in binding that is at least 30 times more favourable than for either unit alone.

Yitzhak Tor, who investigates RNA–small molecule interactions at the University of California, San Diego, US, says that Waters’ results are an important step

forward. ‘Increasing the affinity and selectivity of designer ligands to RNA is challenging and this work elegantly demonstrates the advantage of combining two distinct recognition modes.’ He suggests that similar combined ligand systems could ultimately be useful if they are applied to RNA sequences that are validated as therapeutic targets.

Waters agrees that targeting medically relevant RNA structures is an important future goal in this area. ‘The ability to develop high affinity, high selectivity ligands would open up RNA as a feasible drug target for the treatment of many types of disease, such as HIV,’ she says.

Bailey Fallon

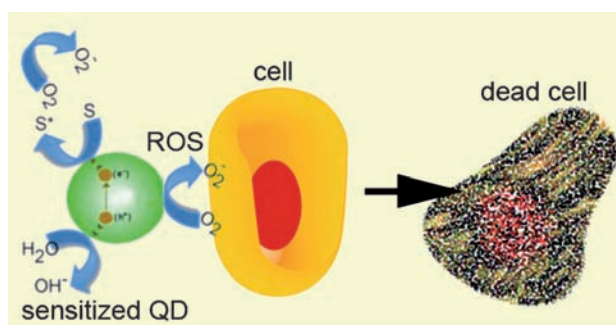
Reference
L L Cline and M L Waters, *Org. Biomol. Chem.*, 2009, DOI: 10.1039/b913024a

Singlet oxygen release suggests cancer therapy use for dopamine-bound particles Topical treatment for quantum dots?

Resolving questions surrounding nanoparticle toxicity has led North American researchers to suggest the particles as a potential skin cancer treatment.

Jay Nadeau from McGill University, Montreal, and colleagues in the US and Canada are investigating using semiconductor nanoparticles, called quantum dots, as photosensitisers – compounds that release reactive oxygen species, such as singlet oxygen, when exposed to light. Photosensitisers can be used in photodynamic therapy, which applies the reactive oxygen species to kill cancer cells. Nadeau's team has measured the reactive oxygen species produced by quantum dots and observed their subsequent effects on cells using a series of assays.

Currently there is a lot of controversy whether quantum dots do produce reactive oxygen species, and if so which ones. Nadeau says she believes her team has finally been able to resolve the issue by standardising experiments. 'Figuring



Dopamine-conjugated quantum dots release cytotoxic reactive oxygen species when treated with UV-to-blue light

Reference
D R Cooper, N M Dimitrijevic and J L Nadeau, *Nanoscale*, 2009, DOI: 10.1039/b9nr00130a

out which assays are best to use will allow you to screen compounds in a way that is valid, so will allow different groups to at least coordinate their results,' she says.

According to Nadeau 'some nanoparticles don't make singlet oxygen but they do when they are connected to small molecules like [the neurotransmitter] dopamine. That opens up a whole other avenue for investigation,' she says. Her team also found that the dopamine-conjugated quantum dots can be used to kill mammalian cells but only on

irradiation with UV-to-blue light. This means the quantum dots are unlikely to be toxic in the body, where the light cannot penetrate, but could have an effect on skin, the researchers claim. They suggest that similar conjugated nanoparticles could potentially be used in photodynamic therapy for skin cancer treatment.

Juan Mareque-Rivas, an expert in fluorescent nanoparticles, from the University of Edinburgh, UK, says 'this is a long overdue investigation. It is nice to see a study in which generation of different reactive oxygen species is demonstrated, quantified and rationalised, and linked to interactions with dopamine – it warns that biomolecules can enhance the phototoxicity of quantum dots.'

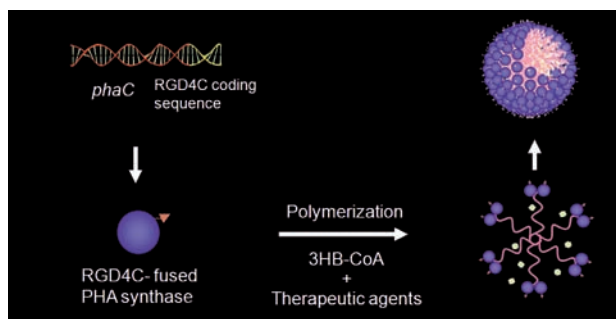
Nadeau's team next plans to move the project into an in vivo melanoma model, to see if dopamine-conjugated quantum dots collect in tumours. Further plans include using quantum dots to develop a cream for healing surgical wounds. *Jennifer Newton*

Protein-polymer species forms nanocarriers that recognise breast cancer cells A biological approach to drug delivery

An all-in-one approach to prepare tumour-targeting polymer spheres has been developed in Korea.

Polymeric micelles made from protein-polymer hybrid materials are promising for drug delivery as the hollow spheres can surround and protect the therapeutic compounds until they reach their target. Typically, the micelles are self-assembled in solution, but they need to then be functionalised with specific ligands to improve their delivery efficiency, making the process lengthy and complicated.

Now, Young-Rok Kim and co-workers from Kyung Hee University, Yongin, have developed a single-step procedure to make nanocarriers that target cancer cells. They achieved this by exploiting a key feature of the enzyme PHA synthase, which catalyses polyhydroxyalkanoate (PHA)



A modified polymer-synthesising enzyme forms micelles with its PHA product

Reference
H-N Kim *et al*, *Chem. Commun.*, 2009, DOI: 10.1039/b912871a

biosynthesis. 'PHA synthesised by PHA synthase remains covalently attached to the enzyme,' explains Kim. 'I thought that this could be an excellent way of synthesising a protein-polymer hybrid.' The group modified PHA synthase with an amino acid sequence that targets tumours by recognising integrin, a cancer-specific marker. They found that the resulting micelles bound

effectively to breast cancer cells.

Vladimir Torchilin, director of the Center for Pharmaceutical Biotechnology and Nanomedicine at Northeastern University, Boston, US, says Kim's method 'is an interesting idea.' However, he warns that 'the problems with more traditional approaches are not that serious,' so the approach may not supplant current methods.

Kim agrees that traditional approaches might be better for functionalising nanocarriers with relatively simple ligands, but adds that 'our approach is suitable for introducing more elaborate functionalities to the nanocarrier, which is hard to achieve with current methods. I believe this will provide much more freedom in designing new macromolecular architectures with precise biological functionality.' *Bailey Fallon*

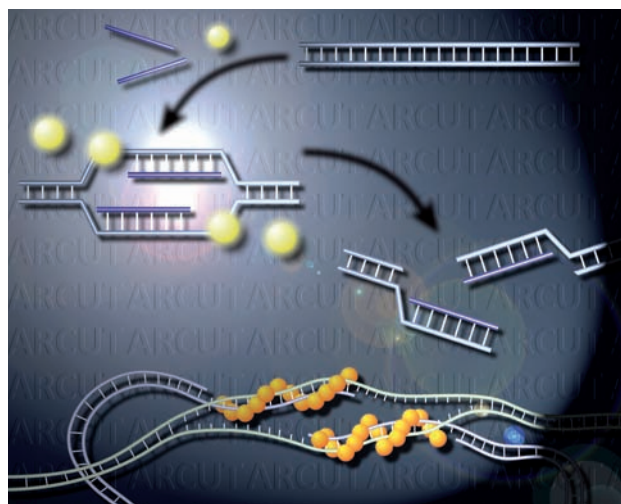
DNA scissors cut human genomic DNA at one target site

Cutting and pasting with the human genome

A DNA cutting tool that can manipulate human genomic DNA could ultimately find applications in gene therapy, say Japanese scientists.

Makoto Komiyama, Narumi Shigi and colleagues at the University of Tokyo recently made the DNA cutter – ARCUT – and used it to cut bacterial DNA at one target site. Now they have shown that it can be tuned to cut human genomic DNA selectively and also to repair it.

ARCUT consists of a cerium(IV) complex which cuts the DNA and a recognition system of peptide nucleic acids, which resemble natural nucleic acids but with a peptide rather than a sugar backbone. The cutter's target site is predetermined by base pairing between the DNA being cut and the bases in the cutter, which can be easily designed to bind a specific scission site. This is currently not possible with naturally occurring DNA cutting enzymes, which cut the genome repeatedly every 44 or 46 base pairs (approximately 700 000 times in human DNA). ARCUT's selectivity meant that the Tokyo team was able to use the cutter to target one site in human genomic DNA – a system 1000 times larger than the *Escherichia coli* DNA



they tested previously.

The researchers have also shown that ARCUT can promote homologous recombination, a process in which nucleic acid fragments are exchanged between lengths of DNA. Whilst several technologies already exist that do this by introducing double strand breaks in DNA, their design and preparation is often difficult and slow. This is because they use protein based nucleic acid cleaving enzymes which recognise the

DNA target site through complex protein–DNA interactions. ‘We have been working on chemistry based artificial cutting enzymes believing that they could be the solution to these problems,’ says Komiyama.

Peter Nielsen works with peptide nucleic acids at the University of Copenhagen, Denmark, and is an expert in DNA recognition and gene targeting. He comments that, although further work is needed to test ARCUT *in vivo*, it is an exciting breakthrough. ‘The DNA cleavage system is very interesting, being a truly chemical system with good efficiency,’ he says. ‘It is also interesting in connection with regimes for gene repair.’

Indeed, the team has already used ARCUT to repair damaged DNA in human cells. The next step for the group is to apply the system *in vivo* so that it can be used for gene therapy and preliminary experiments have been encouraging. Komiyama's team has demonstrated that blue fluorescent protein incorporated into the human genome can be converted to its green analogue using ARCUT-promoted homologous recombination.

Philippa Ross

ARCUT cleaves DNA at a target site allowing further manipulation such as in DNA repair

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 H Katada *et al*, *Chem. Commun.*, 2009, DOI: 10.1039/b912030k

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An ultrasensitive DNAzyme-based colorimetric strategy for nucleic acid detection

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Read more at www.rsc.org/highlightschembiol

Interview

Evolving evolution

*Frances Arnold is using evolution to improve on nature's designs.
Joanne Thomson investigates*



Frances Arnold

Frances Arnold is the Dick and Barbara Dickinson professor of chemical engineering and biochemistry at California Institute of Technology, Pasadena, US. Her work focuses on elucidating the principles of biological design using laboratory evolution experiments.

What inspired you to become a scientist?

I wasn't sure I wanted to become a scientist until I actually became one. I was always good at math and science and that was the easiest way for me to get into Princeton University (US). I did mechanical and aerospace engineering, which had the fewest requirements, but I always thought I'd be a diplomat or perhaps the CEO of a corporation. I had no thought that I'd become a scientist, because I was far more interested in economics and languages. But after college I started working as an engineer in Brazil and at the Solar Energy Research Institute in Colorado (under President Carter, who believed that alternative energy research was important) and found that I enjoyed it. It wasn't until I went to graduate school to get a PhD in chemical engineering, however, that I realised how much I loved biochemistry and that I could have a marvelous career in research.

Darwin's view of evolution describes mutation and natural selection over millions of years. How can you study evolution in the lab in such reduced timeframes?

What we do is not exactly like natural evolution – it's actually artificial selection. Even Darwin (see portrait below) recognised that under strong selection pressure, such as what you impose during plant and animal breeding, large phenotypic changes can manifest themselves very quickly, in just a few generations. I do the same thing, but with molecules, and call it directed evolution. We mutate or recombine genes to create genetic diversity and clone the altered genes into plasmids for expression in a host organism. We screen the mutants for properties of interest, isolate the improved genes, and repeat the cycle until we have bred the molecule(s) we want.

What are you working on at the moment?

I'm interested in engineering new enzymes for bioenergy and 'green' chemistry. Nature is a very good chemist, but there is still room for improvement. For example, cellulases are the enzymes that degrade cellulose into sugars. Cellulose is a very abundant source of sugar but it is really difficult and costly to extract the sugar from it for renewable fuels or chemicals. We need much better enzymes than the ones we find in nature, and I have some ideas for creating those in the laboratory.

I'm also interested in what laboratory evolutionary experiments tell us about how

natural evolution might have occurred, how things evolved in the natural world.

You construct synthetic enzymes. If you could make a synthetic human, what new or improved feature would you try to engineer and why?

Great wisdom, for obvious reasons.

What is your greatest achievement so far?

I think that this must be helping to educate the brilliant students and postdocs who come to the California Institute of Technology. I've been there for 24 years and I've had the pleasure of interacting with well over 100 of some of the smartest young scientists and engineers in the world. If I can help inspire them to use their remarkable brains to solve important problems, and enjoy the process, I feel I have done something really useful.

How has the global recession affected science?

Personally, I have not really suffered. I've never had much trouble getting funding. But I do see that the recession has limited the job market for graduates. The opportunities for young people are fewer now, in industry as well as in academic research. I hope that does not dampen their enthusiasm for tackling the most important problems.

You travel the world attending conferences. Which destination is your favourite?

I love the whole world – I can't choose a favourite. Five years ago, I took all three of my sons around the world for a whole year. They went to school in Australia, Africa, and Wales that year. I love to go to new places, and find that almost every place has something wonderful to offer.

What do you do in your spare time?

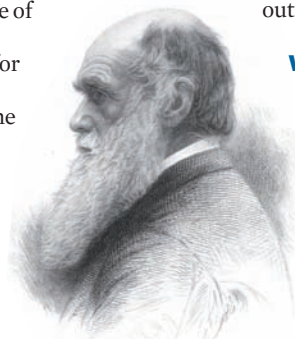
I have three sons, whom I adore. I enjoy doing things and traveling with them. Scuba diving and yoga are great. I also have a rustic (no water, no electricity) cabin in the mountains where I go to relax or work. I am deeply concerned about climate change and renewable energy and spend considerable time outside of my research on these issues.

What would you be if you weren't a scientist?

I would love to be a musician and composer, but sadly don't have any real talent for it.

For which scientific discovery would you like to have been responsible?

The theory of natural selection, of course!



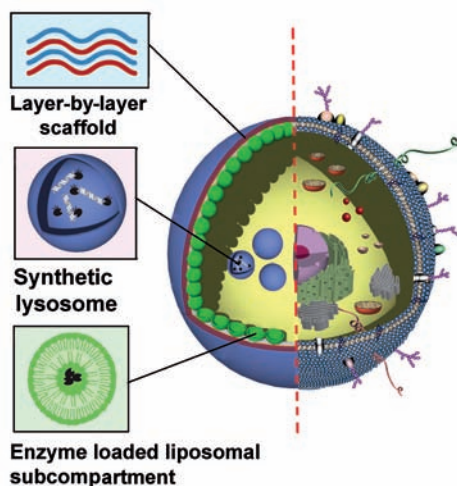
Making synthetic cells

Cell and organelle mimics typically perform one simple function. Frank Caruso and team at the University of Melbourne, Australia, contemplate more complicated systems

Artificial cells and organelles are expected to become powerful therapeutic tools to perform missing or lost cell functions – essentially to make, convert or degrade biomolecules. Amongst their potential applications, replenishing absent or malfunctioning enzymes is a valuable goal as this might provide a long-term solution for chronic diseases. But the field is still in its infancy, with the most successful examples of synthetic cells and organelles typically performing only a single, simple function.

Nevertheless, recent efforts have led to substantial improvements in the design of these synthetic microreactors. In particular, advances have been seen in more structurally stable scaffolds to house the synthetic machinery, enhance reagent and nutrient exchange between the vessels and their surrounding environment, and in introducing subcompartments within the vessels, allowing researchers to conduct multiple, spatially separated and/or continuous reactions.

The field has also been boosted significantly by the advent of polymer capsules assembled by layer-by-layer techniques. In this procedure interacting polymers are deposited sequentially onto a sacrificial colloidal template which is eventually removed. Two prominent polymer pairs that form stable, micrometre- or smaller-sized capsules are based on poly(allylamine hydrochloride)/polystyrene sulfonate and poly(*N*-vinyl pyrrolidone)/poly(methacrylic acid). While the former capsules are not biodegradable and have potential use in creating organelles with extended lifetimes, the latter polymer pair is used to obtain



Synthetic mimics (left) can share many similarities with biological cells (right)

biodegradable capsules stabilised by deconstructible disulfide linkages.

Progress in cargo loading has meant that peptides, nucleic acids and intact proteins can be trapped inside such polymer capsules, making them particularly promising candidates in the design of therapeutic artificial cells and organelles. The first examples of enzymatic reactions within the capsules have brought these vehicles one step closer towards this. The most well studied class of these reactions involves the enzyme-catalysed conversion of small molecules, as the capsules' semipermeable nature allows small substrates and products (for example ions) to diffuse in and out while the larger macromolecules are blocked.

A number of enzymes have now been successfully encapsulated, retained their activity and performed their function within capsules. We recently reported DNA degradation triggered by a nuclease within a polymer capsule, a function reminiscent of that of the cellular lysosome, an organelle containing several digestive enzymes. This was one of

the first examples of a layer-by-layer assembled capsule mimicking an organelle.

A nature-inspired approach towards synthetic reactors that allow multiple, spatially separated and parallel reactions, requires that the vessels be subdivided. Specific examples include two-compartment polymer capsules, smaller lipid or polymeric vesicles embedded in larger vesicles, and smaller capsules embedded in cross-linked gel beads.

We have developed an approach to obtain polymer carrier capsules with thousands of liposomal subcompartments (see green spherical structures in figure). Termed capsosomes, these vehicles preserve the positive features from both systems – the polymer hydrogel carrier capsule provides a structurally stable scaffold, while the liposomal subcompartments trap and protect small and/or fragile biomolecules. Capsosomes can retain a model enzyme and preserve its activity for at least two weeks.

The progress in the design of layer-by-layer-derived polymer capsules, including the choice of building blocks to obtain stable capsules, the creation of subdivided systems, and the successful encapsulation of enzyme-catalysed reactions, illustrate the potential of these vehicles as synthetic cell and organelle mimics. While many challenges still need to be addressed, including creating systems that can self-replicate, self-repair, and recognise a target, the field is undoubtedly on the verge of creating medically relevant examples.

Read more in the Minireview 'Polymer hydrogel capsules: en route toward synthetic cellular systems' in issue 1, 2009, of *Nanoscale*.

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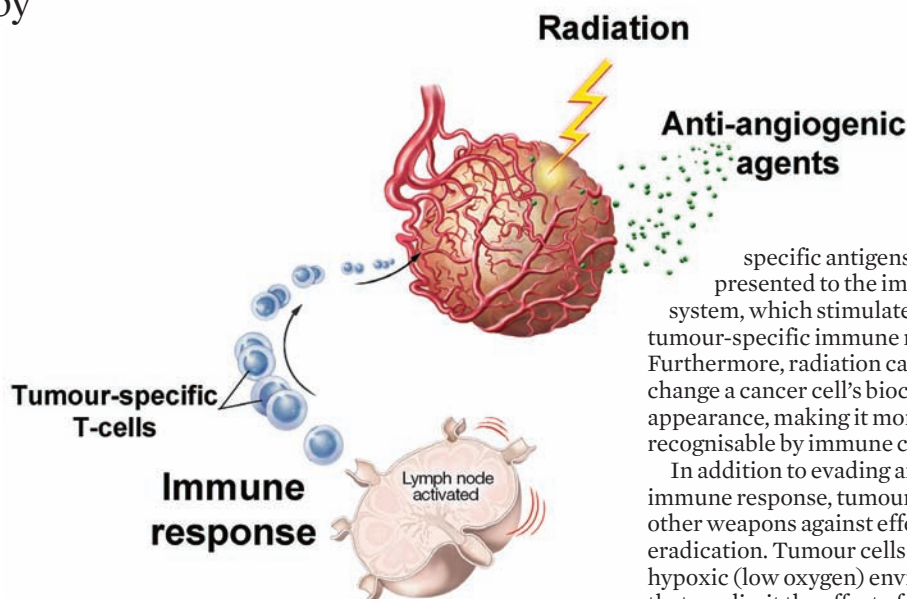
Triple therapy to target tumours

Drs Bernstein, Kamrava, Camphausen and Hodge at the National Institutes of Health, Bethesda, Maryland, US, explain why good things come in threes when it comes to cancer therapy

Using several concurrent approaches to treat a single disease is not a novel concept anymore. When treating some of the most common illnesses affecting people today, the best outcomes are often achieved with more than one therapy or medication, especially when those therapies have different mechanisms of action.

For instance, treatment for hypertension frequently starts with a diuretic to decrease the fluid volume in the blood stream, and so lower the arterial pressure. If blood pressure remains uncontrolled, a beta-blocker may be added to the regimen. This lowers the blood's force as it is pumped through the vessels. Along with this, an angiotensin-converting enzyme (ACE) inhibitor may be prescribed to dilate the arteries. Similarly, controlling hyperglycemia in diabetic patients often requires combining one medication to stimulate the pancreas to release more insulin with another medication to prevent the liver from releasing stored sugar. This approach of targeting different aspects of a disease with different drugs often succeeds because the actions of one agent complement, or even enhance, the actions of the second or third.

This approach is now being applied in the challenging field of cancer treatment. Because some single therapies have shown limited clinical benefit, oncologists are increasingly using combination therapies to try to improve outcomes for cancer sufferers. For example, many patients first have their tumours removed surgically, then go on to receive postoperative chemotherapy, radiation therapy, or a combination of both. Unfortunately, while this and other advances in cancer



Combining radiation therapy, immunotherapy, and antiangiogenesis exploits weaknesses in cancer cell defences

treatment have shown promising results, malignancy has remained the second most common cause of death for decades, making cancer research one of the most dynamic fields in medicine.

In one potential approach, three different treatments – radiation therapy, immunotherapy (harnessing the immune system), and antiangiogenesis (reorganising the tumour's blood supply) – could be applied to treat cancer. The rationale is the same as for the combinatorial approach to treating hypertension and diabetes. Each of these three cancer therapies affects a different aspect of a tumour's biology and microenvironment, which could facilitate and enhance the actions of the other two.

Cancer cells can grow and replicate stealthily, without setting off the usual alarms that activate the host's immune system. Besides its traditional role of directly killing tumour cells, radiation can also be used to sound these alarms and activate an immune response. Exposing a tumour to radiation can break the silent barrier and cause the tumour to release unique proteins. A rich supply of tumour-

specific antigens is then presented to the immune system, which stimulates a tumour-specific immune response. Furthermore, radiation can change a cancer cell's biochemical appearance, making it more readily recognisable by immune cells.

In addition to evading an immune response, tumours have other weapons against effective eradication. Tumour cells create a hypoxic (low oxygen) environment that can limit the effect of various therapies. This has spurred research into angiogenesis inhibitors, which normalise blood vessels in the tumour and limit hypoxia. By increasing oxygen availability and blood supply, antiangiogenic agents can both enhance the effects of radiation therapy and facilitate immune cells' access to the tumour.

Preclinical and clinical studies support the rationale for combining antiangiogenic agents with radiation and immunotherapy in cancer treatment. This particular combination of therapies not only exploits weaknesses in cancer cell defences, but also boosts the strengths of the individual methods. We are just beginning to recognise the potential benefits of this combination, but the evidence suggests that it provides a reasonable option for cancer patients and deserves further investigation.

Read more in the review 'Combining radiation, immunotherapy, and antiangiogenesis agents in the management of cancer: the Three Musketeers or just another quixotic combination?' in Molecular BioSystems.

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Essential elements

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Two new titles have joined the well established RSC Publishing journal portfolio with the online publication of issue 1 of *Analytical Methods* and *Nanoscale*.

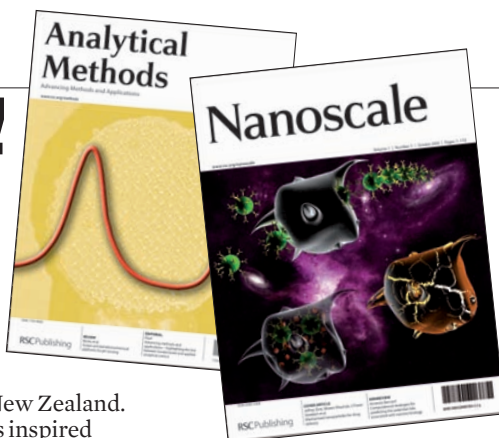
Analytical Methods (www.rsc.org/methods) highlights new and improved methods for the practical application of analytical science. The journal's first issue showcases articles reflecting *Analytical Methods'* highly topical scope on new applications of analytical science and technology which address current global challenges such as securing food supplies, improving and preserving human health, creating and maintaining sustainable feedstocks and sustaining the management of water and air quality.

Packed with the highest quality, high-impact research, that readers can expect in *Analytical Methods*, issue 1 includes a paper on Raman

spectroscopic prediction of the solid fat content of anhydrous milk fat by Keith Gordon and colleagues from the University of Otago, Dunedin, New Zealand. The cover image is inspired by an article on screen printed electrochemical platforms for pH sensing by Craig Banks and colleagues of Manchester Metropolitan University, UK.

Nanoscale (www.rsc.org/nanoscale), published in collaboration with the National Center for Nanoscience and Technology, Beijing, China, showcases important and high quality nano-research, providing a forum that will be essential reading for all scientific communities working at the nanoscale.

The 20 articles in issue 1 cover a broad spectrum of exciting work from some of the very



best research groups in the field, including those of Fraser Stoddart, C N R Rao, Markus Antonietti, Kazunari Domen, Luis Liz-Marzán and Naomi Halas.

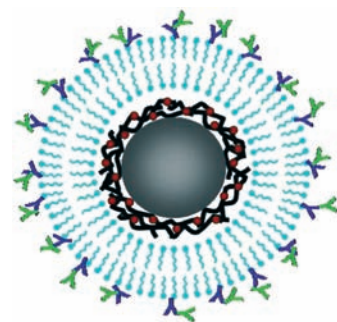
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One of the Top 5 – a bioinspired colloidal system

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