

## Pacifichem 2010: Excerpts from a Student's Diary

Peter G. K. Clark

School of Chemical & Physical Sciences, Victoria University, PO Box 600, Wellington 6140  
(e-mail: [peter.clark@vuw.ac.nz](mailto:peter.clark@vuw.ac.nz))

### Note from the 2010 NZIC President

As one of the seven sponsoring societies of Pacifichem, the NZIC holds a privileged position among the many chemical societies represented at the Congress. The NZIC has a permanent representative on the organizing committee (currently Prof Rob Smith - University of Otago) and the NZIC President is invited to attend the Opening Ceremony in an official capacity and then a dinner on the final night of the conference with the organizing committee and the Presidents and Chief Executives of the other six sponsoring societies (ACS, CIC, JCS, CCS, KCS, RACI). At Pacifichem 2010, the NZIC President also attended a meeting of the Asian Chemical Editorial Society (ACES), the governing body of Chemistry - An Asian Journal, of which NZIC became a member in 2008, the first time an NZIC representative had been able to attend an ACES meeting.

Despite the fact that NZIC delegates are heavily diluted by their counterparts from the ACS, CIC and especially the JCS, the NZIC has approximately proportional representation across a wide range of fields from relativistic computational chemistry to organic synthesis and environmental chemistry.

Mark Waterland  
President in attendance

### Introduction

The International Chemical Congress of Pacific Basin Societies, *Pacifichem*, is one of the largest chemistry conferences in the world. Composed of the chemical societies of the Pacific Basin and held every five years in Honolulu, the Congress aims to promote scientific exchange for a healthy and sustainable future. During December 15-20 last, Pacifichem 2010 hosted 13 areas of chemistry, 239 symposia, 12,844 technical presentations and 12,751 scientists.

As one of the largest chemistry conferences in the world, a group of four PhD and MSc students from Victoria University, out of the 76 Kiwi attendees, decided this might be a good one to cut our teeth on. Due to flight availability, we *had* to arrive four days early and have a short holiday in Honolulu. Having surveyed the view from Diamond Head crater, swam with the sea life amongst the Hanauma Bay coral, visited Chinatown and lounged around at Waikiki Beach, and whilst drinking from coconuts and sipping Mai Tais, we decided it was a hard life being a student. We learned a few lessons during our time there: the sugar coating of breakfast cereal can be removed by pre-washing with water; mechanically-separated turkey franks are surprisingly good; and the art of *FreeCon* - walking close to the open doors of shops (Gucci, Chanel and Hugo Boss in particular) to get free waves of air-conditioning. All this aside, we were there for a conference.

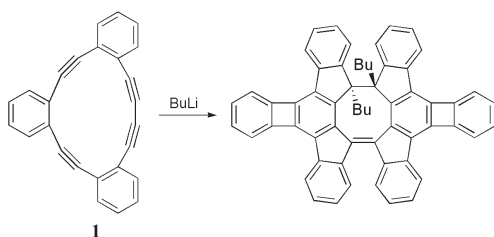
### Early Days

Given my diverse interests, I attended a wide range of talks. The first was by Prof. Tehshik Yoon (University of Wisconsin), who is investigating using visible light to photocatalyze organic reactions by use of a  $\text{Ru}(\text{bpy})_3^{2+}$  catalyst. Prof. Juan Scaiano (University of Ottawa) presented related work, but utilizing surface plasmon fields of gold nanoparticles instead. In the presence of a mono-

mer precursor, cross-linked acrylic shells form around the nanoparticles and from the diameter the field effect was estimated at 8-10 nm. Meanwhile, Prof. Vaidhyanathan Ramamurthy (University of Miami) presented work on using weak non-covalent forces to control photochemical reactions. This included encapsulating reagents in cavities such as provided by  $\gamma$ -cyclodextrin, and crystallization with hydrogen-bonding species such as thiourea.

The Pacifichem Congress plenary was delivered by Prof. Paul Corkum (University of Ottawa), entitled *Catching Electrons with Light*. Whereas the molecular orbitals we all know are 90% *probability surfaces*, Corkum is now using attosecond laser pulses to help create images of *actual* electrons orbiting molecules.<sup>1</sup> Furthermore, his more recent work involves following chemical reactions as they occur.<sup>2</sup> I cannot do the man or his work justice in trying to present the science here, so I encourage you to read the cited papers.

Prof. James Wuest (University of Montreal) has taken highly-crystalline hexaphenylbenzene-based compounds and found ways to structurally inhibit crystal formation, *as all good crystal engineers should be able to*, he added. Prof. Clémence Corminboeuf (Ecole Polytechnique Fédérale de Lausanne), amongst her interest towards a more physical understanding of chemical concepts, presented work assessing  $\pi$ -conjugation effects by computationally comparing discrete resonance structures with their conjugated-counterparts. This work could have applications in the field of Möbius aromaticity, where there is much conjecture over aromatic parameters. In the same symposium, entitled *Designed pi-Electronic Systems* Prof. Yoshito Tobe (Osaka University) showed serendipity is always a force in chemistry with the dehydrobenzo[14]annulene (**1**) undergoing unexpected dimerization (Scheme 1). As to the mechanism: I don't know, he said with a laugh.



**Scheme 1.** Tobe's unexpected dimerization

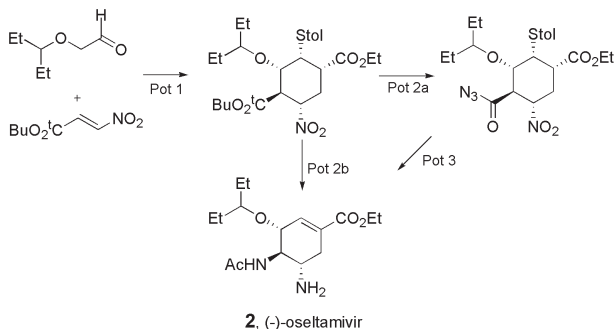
## Masters of Synthesis

### One-Pot Synthesis - Yujiro Hayashi

Tamiflu, the phosphate salt of oseltamivir (**2**), is an antiviral drug that can slow the spread of influenza virus and was hurriedly stockpiled by governments during the *bird* and *swine flu* pandemics. Commercial production was originally based on shikimic acid, a biosynthetic intermediate of low natural abundance and of low extraction yield, leading to supply problems. A short, high-yielding, inexpensive synthesis was therefore required. Alternative total syntheses were put forth by many chemists, each surpassing one another in yields and steps.<sup>3</sup> The record was last held by Barry Trost and Liang-Deng Nie, with eight-step syntheses of 30%<sup>4</sup> and 47%<sup>5</sup> overall yields, respectively, until Prof. Yujiro Hayashi came on the scene with a three-pot, 57% yield total synthesis.

Utilizing a mixture of Michael, retro-Michael and Horner-Wardsworth-Emmons reactions, as well as functional group modifications and a Curtius rearrangement, and relying upon evaporation of excess reagents and solvents, (-)-oseltamivir could be obtained from three-pots without the need to exclude water or air and need for but one column chromatography (Pots 1, 2a and 3, Scheme 2).<sup>6</sup> Having presented this during his talk, Prof. Hayashi then asked the question: *Why not two-pot?* By modifying reagent choice to allow solvent compatibility, a two-pot synthesis of oseltamivir can be completed with a 60% yield and a single column chromatography (Pot 1 and 2b, Scheme 2). Prof. Hayashi then asked another interesting question: *Why not no columns?* Replacing the single

column with two acid-base workups, Prof. Hayashi has also now synthesized oseltamivir in three pots with a 60% yield and *column-free*. This is the sort of work that synthetic chemists talk about in their sleep. On a personal note, I sadly mean that literally.

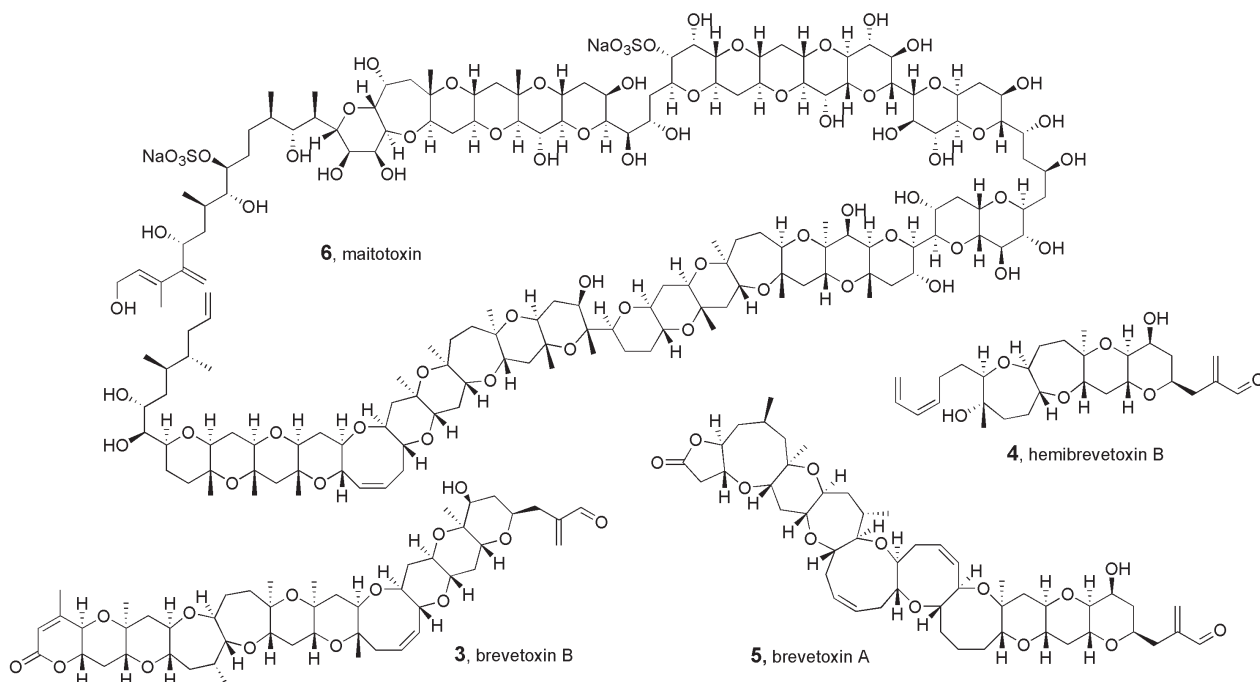


**Scheme 2.** Hayashi's syntheses of oseltamivir (**2**).

### Marine Polyether Biotoxins - K. C. Nicolaou

You know a superstar is talking when you arrive an hour early and there is already standing-room only. Prof. K. C. Nicolaou (Scripps Institute) began his talk on marine polyether biotoxins by highlighting his progressive baldness over his career. He made many comparisons to his friend, Masakatsu Shibasaki, who was sitting on the floor after vacating his seat for a blonde, female student standing nearby (some things never change). Nicolaou then presented his vision of synthetic chemistry: *We do it to advance the art of total synthesis for our own sake and for the excitement it provides... Musical notes combine to create a melody. Similarly, chemical reaction notes combine to create natural product melodies.*

This study began on a day in November 1981, when he came across a paper reporting a new marine polyether called brevetoxin B (**3**), a highly-potent biotoxin. Having seen its molecular complexity, immediately he locked himself in his office and tried to work out how to make it. He emerged two hours later *with no clue*. The epoxide chemistry needed to synthesize the molecule simply



did not exist. So he developed some. Eight new synthetic methods and twelve years later, the total synthesis of brevetoxin B was complete with its report subtitled *A Twelve-Year Odyssey in Organic Synthesis*, lending credence to the monumentality of the feat.<sup>7</sup> Hemibrevetoxin B (**4**) also was synthesized along the way,<sup>8</sup> followed by brevetoxin A (**5**).<sup>9</sup> This left the trifling matter of synthesizing a related highly-potent marine polyether, called maitotoxin (**6**).

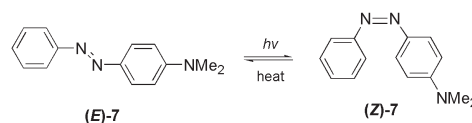
When I first saw this compound as an undergraduate student, I laughed because I knew no-one would ever synthesize it. Polyether **6** is the largest non-biopolymeric secondary metabolite ever isolated, with a molecular mass of 3422 g/mol; it is also the most complex, with 32 rings and 99 elements of stereochemistry. Needless to say, when Nicolaou first mentioned the name maitotoxin in his talk, I nearly choked. Rather than diving into the total synthesis, as I expected, he presented molecular calculations on a section of the molecule to settle a disagreement over the stereochemistry at two centers<sup>10</sup> - and here it is pertinent to point out that part of a review article was dedicated simply to summarizing structural elucidation attempts.<sup>11</sup> But, having obtained an answer, he said *these are just calculations*, so he synthesized the relevant fragment of the molecule to support his finding.<sup>12</sup> Having done this, he decided to synthesize another fragment<sup>13</sup> or two.<sup>14</sup> Following years of research and the development of further novel reactions, he now stands four rings, and some funding, short of the total synthesis of **6**, *that is, if one desired to make it*, he added whilst sipping some water. Being the young, impressionable youth that I am, I shall never forget that talk. An interesting reflection on Nicolaou's career is available.<sup>15</sup>

### The Mid-Congress Blur

Prof. Ei-ichi Negishi (Purdue University), the 2010 Chemistry Nobel Laureate, mentioned off-hand during his talk that, having just returned from Stockholm, he had his Nobel medal in his wallet. There was a subsequent 10-minute delay in his talk whilst members of the audience got photos of him with said medal. Prof. Robert Grubbs (CIT), of catalyst and 2005 Nobel-prize fame, could be seen between the heads of people crowding out the door at his *standing room only* talk, as was Prof. Eric Jacobsen (Harvard University), famous for the Jacobsen epoxidation.

Since my school days, I have been fascinated with hydrogen as a clean and renewable alternative to fossil fuels. Despite images of former-Governor Arnold Schwarzenegger standing proudly beside his hydrogen-powered Hummer, a remaining hurdle to this technology is the green generation of hydrogen, which is now being solved by splitting water using sunlight. I attended a number of talks directed towards achieving this, using various colloidal metals and ligands to optimize the absorption of light and the redox reactions. Rather than inaccurately present their work here, I direct you to the work of Stefan Bernhand (Carnegie Mellon University), Kazuhiko Maeda (University of Tokyo) and Felix Castellano (Bowling Green State University).

Back at the Hilton, Prof. Hideko Koshima (Ehime University) presented her work on microcrystals that bend upon UV irradiation. Composed of (*E*)-(4-dimethylamino)azobenzene [(*E*)-**7**] they undergo photoisomerization to the *Z*-form [(*Z*)-**7**] upon irradiation. This results in an observable bending of the plate-like microcrystals (Scheme 3). The work of Terunori Fujita (Mitsui Chemicals) was also presented, in which he described the ways found to industrially convert bioethanol into propylene for use in polymer manufacture. Elsewhere, Bernd Ondruschka (University of Jena) extolled the values of sonochemistry, the use of acoustic cavitation - sound wave-generated bubble formation and collapse - to produce chemical and physical changes. When used in biodiesel production, yields increased from 5.5% to 77.3%; one can understand his support.



**Scheme 3.** Photoisomerization that results in crystal bending.

## Emerging Areas of Chemistry

### Flow chemistry - Steven Ley

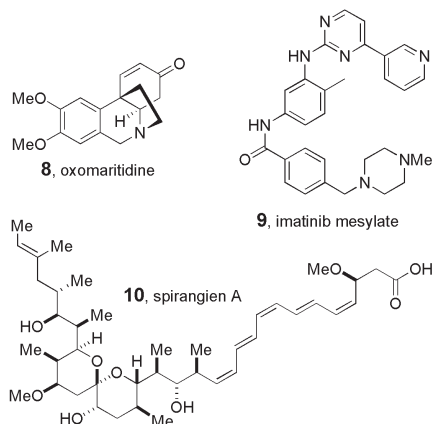
Continuous-flow chemistry is shaping as a new dimension in organic synthesis. The procedure is one where reactions occur in a continuously-flowing stream and involves pumping dissolved reagents through narrow units with different chemical functions that induce chemical transformations.<sup>16</sup>

These units can range from columns packed with immobilized reagents or catalysts to microwave and hydrogenation reactors to scavenging cartridges or chromatographic columns. Combining these in a linear sequence can allow the total synthesis of some natural products to be completed in a continuous operation.

This field has largely been pioneered by Prof. Steven Ley at Cambridge University. His flagship synthesis is that of the alkaloid oxomaritidine (**8**)<sup>17</sup> This utilized azide-exchange resins, polymer-supported phosphines, flow hydrogenators and microfluidic reaction chips, amongst others, to give the alkaloid in 40% yield. There was a single product-handling step, namely the highly strenuous act of swapping solvents from THF to DCM. Some of the key units developed by the Ley group are tube-in-tube gas flow reactors, which deliver safe levels of dissolved gases, and IR & UV sensors that match the delivery concentration of a reagent to the concentration of product flowing through the system, which disperses during passage through the reactors.

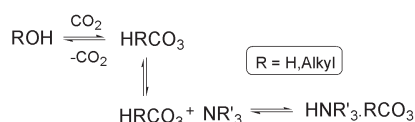
The work has been so successful that drug companies now seek him out to attempt syntheses of their pharmaceuticals. The flow-based synthesis of the anticancer drug imatinib mesylate (**9**) is a prime example.<sup>18</sup> For this, a solvent switch was developed, removing a lower boiling solvent by bubbling through an inert gas. The Ley group is currently targeting the antifungal spirangien A (**10**) in an early example of flow chemistry directly competing with benchtop chemists. Ian Paterson, also of Cambridge, completed

the total synthesis of **10** in 2008, in 18 steps and a 2% yield.<sup>19</sup> So far, Ley has completed a 150 g synthesis of a key building block, run by a student's cell phone from a remote location. Given the automation and speed possible with flow chemistry, this certainly appears to be the future of industrial pharmaceutical production. A recent reflection of Ley's natural product work has appeared.<sup>20</sup>



### Switchable Solvents - Philip Jessop

Prof. Philip Jessop (Queen's University) has worked towards developing solvents with properties that can be changed upon command. Organic reactions are usually performed in solution, but product separation is then required. Distillations require volatile solvents and energy, adding antisolvent generates more solvent waste and extraction into another solvent *still* requires separation. A new solution to this is *switching* the solvent from one type to another. Prof. Jessop is developing solvents that change their polarity, reversibly, upon addition or removal of CO<sub>2</sub>. The equilibria between carbon dioxide and water or alcohols generate acidic species that protonate nitrogen atoms of the solvent and increase its polarity (Scheme 4). These equilibria can be reversed by bubbling through an inert gas or heating. To date, three sorts of switchable solvents have been investigated.



**Scheme 4.** Equilibria occurring within a switchable solvent.

Switchable-polarity solvents, as their name suggests, change polarity upon addition or removal of CO<sub>2</sub>. Typically, these are mixtures of an amidine base and an alcohol that are inherently nonpolar, but form ionic liquids upon addition of CO<sub>2</sub> (Scheme 5i).<sup>21</sup> Switchable-hydrophilicity solvents change their miscibility with water as a result of polarity change (Scheme 5ii).<sup>22</sup> Composed of bi-

phasic mixtures of non-polar amidine and water, upon addition of CO<sub>2</sub> they form a monophasic, high-polarity solvent, which affects the solubility of any solutes originally in the amidine. These two approaches have been used in the extraction of soy bean oil from soy bean flakes.<sup>23</sup> Commercially, the oil is extracted using a hexane solvent (*flammable, high insurance costs, hazards- toxicity, narcoticity... I can't even pronounce the rest of them*), which is then distilled off. Switchable solvents can be used to extract the oil, which, upon addition of carbon dioxide, separates out as a pure compound. After decantation and carbon dioxide removal, the solvents are returned to their original state ready for reuse.

The newest approach involves switchable water – a reversible *salting out* approach. When a homogenous solution of water and an organic solvent, such as THF, with an uncharged diamine additive is exposed to CO<sub>2</sub>, the additive becomes charged, raising the ionic strength of the water, and hence immiscibility with the THF (Scheme 5iii).<sup>24</sup> Although salting out approaches have been frowned upon by industry owing to the irreversible generation of large quantities of salty water, this system can be reversed simply by removing carbon dioxide. This could find use in organic synthetic chemistry due to the ability to extract catalyst or product by blowing on the reaction. In addition to use in industrial settings, this area of chemistry also could lead to some interesting advances in the scope of solvent-phase reactions.

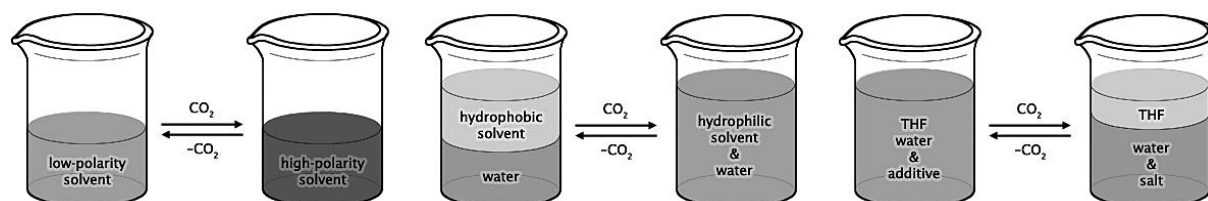
### Artificial Enzymes - Ronald Breslow

Enzymes are the synthetic chemists of the natural world. They catalyze specific reactions in aqueous environments containing many different species and with complete regio-, chemo- and stereoselectivity. The key to this is their ability to form, through folding and interactions, very specific binding pockets in space that position key catalytic moieties and exclude water and other molecules. Artificial enzymes, therefore, may be able to replicate these activities, but without the concerns of hydrolysis or *death* of the enzyme. Towards this aim, Prof. Ronald Breslow (Columbia University) has been attempting to synthesize artificial enzymes. Using biology as an inspiration (not as a blueprint- *a jumbo jet is not just a scaled up pigeon*),<sup>25</sup> modified polyethylenimines (PEIs, **11**) are used as enzyme surrogates. These polymers self-assemble in water to form micelle-like structures, with water-excluded cores that act as binding domains. These cores promote the hydrophobic binding of substrates and coenzymes, molecular entities that associate with enzymes and contain key functional groups for enzymatic catalysis.

i) Switchable-polarity solvents

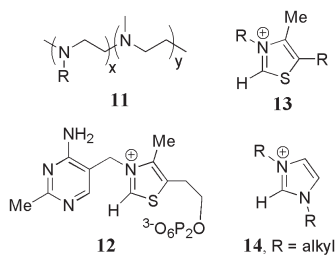
ii) Switchable-hydrophilicity solvents

iii) Switchable water

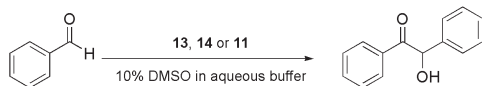


**Scheme 5.** Equilibria of the different types of switchable solvents; reprinted from:

<http://www.chem.queensu.ca/people/faculty/jessop/switchable.html> with permission from Philip Jessop and Darrell Dean.



Thiamine diphosphate (**12**) is a coenzyme that, by way of a stable, nucleophilic carbene generated at the C-2 position, can catalyze condensation reactions that generate  $\alpha$ -keto alcohols. Thiazolium **13** and imidazolium **14** synthetic equivalents of this, therefore, were trialed in a benzoin condensation (Scheme 6).<sup>26</sup> The presence of **13** or **14** alone can catalyze the benzoin condensation, but in the presence of **11** their alkyl chains promote incorporation into the *enzyme* core, completing the artificial enzyme, and a 3000-fold acceleration in reaction rate is seen. Although the field is still young, designed artificial enzymes with all the synthetic abilities of natural enzymes may one day be achievable. We are now one step closer to taking biochemistry back from the biologists.



**Scheme 6.** The benzoin condensation

## Social Gatherings

The conference was not all work and no play! The evenings rapidly became filled with receptions and functions. The opening ceremony, with traditional Hawaiian dances that felt reminiscent of dances from home, was followed by a large reception on the lawn of the Sheraton Hotel. Another reception was charged with ushering in the International Year of Chemistry, 2011, at the lagoon of the Hilton Hawaiian Village (Yes, the Hilton has its own lagoon - and penguins). In addition, the Law Division of the ACS generously hosted an open-bar reception by the pool of the Hyatt Hotel (I thank the ACS for numerous Mai Tai's). On a more personal level, the symposium on *New Dimensions of Green Sustainable Chemistry* had a small reception for attendees. During this time, we got to chat,

over a few beers and many chicken kebabs, with Prof. Chris Strauss, who can be thanked for the existence of microwave organic synthesis. The photograph (see below) was taken towards the end of the reception, and pictures Hemi Cumming, a VUW PhD student, and the author with Chris Strauss, C-J Li, an eminent organic chemist in Canada, Tamim Braish, director of pharmaceutical process discovery at Pfizer, and Shu Kobayashi, of water-compatible Friedel-Crafts-catalyst fame. The symposia-related receptions are a great way to meet people in your area, and I simply wish there were more.

## The Final Days

Prof. C.-J. Li (McGill University), in a symposium entitled *C-H functionalization*, presented his group's work towards forming C-C bonds from C-H bonds using cross-dehydrogenative couplings that use cheap catalysts and oxidants. This novel reaction avoids protection-deprotections, whilst allowing catalytic functionalization of C-H bonds and direct C-H/C-H couplings. After an hour-long tour through the reactions they have explored, from using magnetic nanoparticle catalysts to allow catalyst conservation, to site-specific peptide modifications, he summarized by highlighting that they now had examples of creating C-C bonds from all possible combinations of  $sp$ ,  $sp^2$  or  $sp^3$  C-H-bonded starting materials. After such a relaxed, early-morning talk, it was an awe-inspiring conclusion, and emphasized his position in the Canadian organic synthesis scene.

Jón Njarðarson (University of Arizona) showed that perseverance sometimes is needed in chemistry, by detailing seven different routes he attempted towards the synthesis of the natural product vinigrol. Prof. David Black (University of New South Wales) meanwhile raised the concern that screening for novel reactions should utilize activated models rather than unsubstituted-parent compounds. Finally, as an example of convergent research interests, Prof. Jef DeBradander (Texas Southwestern Medical Centre) was discussing a potential synthetic pathway to the natural product spirastrellolide in one room whilst, minutes before, Prof. Ian Paterson (University of Cambridge) had presented his total synthesis of it just next door.



Symposium Reception. L-R: Hemi Cumming, C.-J. Li, Shu Kobayashi, Tamim Braish, Chris Strauss, Peter Clark. Photo credit - Peter Moore.

## New Approaches in Synthesis

### Contemporaneous Dual Catalysis

Dual catalysis involves two catalysts generating two reactive intermediates that couple to produce a new compound. Being catalytic quantities of reactive intermediates, however, these tend to form byproducts with stoichiometric species present instead. By controlling the rate of formation of the intermediates, chemoselectivity can dominate over concentration effects and the desired product can be formed. In what he has termed contemporaneous dual catalysis, Recently, Prof. Barry Trost (Stanford University) has been able to generate a coupled product from intersecting vanadium- and palladium-catalysed cycles, showing dual catalysis can be a feasible approach.

### Organocascade Catalysis and Collective Total Synthesis

The final talk I attended certainly did not disappoint. Although metal-catalyzed cascades (where products of one cycle feed into another) exist, Prof. David MacMillan (Princeton University) only recently has disclosed the concept of performing these with organocatalysts (Scheme 7).<sup>27</sup> His flagship synthesis of aromadendrane-diol involves a triple-cascade, in which the product of a cross-metathesis cycle feeds into an iminium cycle which then feeds into an enamine cycle, highlighting the synthetic value of this approach.<sup>28</sup>



Scheme 7. Organocascade catalysis

His second novel approach requires changing the mindset of chemists when synthesizing chemical families. Traditionally, specific methods are devised for each member of a family. What MacMillan instead suggests is collective total synthesis - using a general synthesis to a common intermediate, then diversifying. This has benefits towards creating families for biological testing, but also towards families of natural products. The *Strychnos* family, for example, has over 100 members that have been synthesized to date. In soon to be published work from a common intermediate, he achieved the total synthesis of members of this family, which was more efficient than the existing specific syntheses.

### Final Thoughts

Reflecting on Pacificchem 2010 (and a school of fish leaping over my leg on the shore of Hanauma Bay), a few comments come to mind. It was an invaluable opportunity to see and hear research at the forefront of scientific discovery, by the people leading their fields, and I know that I have been inspired to approach my work with renewed vigour and new ideas. The conference fulfilled its aims of facilitating scientific exchange towards a sustainable future, as is clearly visible in the drives towards making chemistry green and with alternative energy technologies. However, these all rely on our current theories of atoms and molecular orbitals being correct. The concept of the atom that we have today has evolved hugely through time, and many theories, subsequently disproven, were at one

point held as truth. With so much of organic chemistry reliant on molecular orbital theory, the question is will this one day be disproven too? With the exponential growth in computational chemistry, it may be only a matter of time until *regular irregularities* induce another evolution in chemistry and our understanding of the world. Only time will tell what Pacificchem 2015 will hold in store for us.

### Acknowledgements

I acknowledge financial support from the Rotary Club of Terrace End Memorial Education Trust and the Wellington Branch of NZIC for making my attendance at the conference possible. I also thank my travelling companions, Hemi Cumming, Jacqui Barber and Peter Moore, for adding to the interest of the trip.

### References

1. Itatani, J.; Levesque, J.; Zeidler, D.; Niikura, H., *et al. Nature* **2004**, *432*, 867-871.
2. Worner, H. J.; Bertrand, J. B.; Kartashov, D. V.; Corkum, P. B.; Villeneuve, D. M. *Nature* **2010**, *466*, 604-607.
3. Gong, J. Z.; Xu, W. F. *Cur. Med. Chem.* **2008**, *15*, 3145-3159.
4. Trost, B. M.; Zhang, T. *Angew. Chem. Int. Ed.* **2008**, *47*, 3759-3761.
5. Nie, L.-D.; Shi, X.-X.; Ko, K. H.; Lu, W.-D. *J. Org. Chem.* **2009**, *74*, 3970-3973.
6. Ishikawa, H.; Suzuki, T.; Hayashi, Y. *Angew. Chem. Int. Ed.* **2009**, *48*, 1304-1307.
7. Nicolaou, K. C. *Angew. Chem. Int. Ed.* **1996**, *35*, 589-607.
8. Nicolaou, K. C.; Reddy, K. R.; Skokotas, G.; Sato, F.; Xiao, X. Y. *J. Am. Chem. Soc.* **1992**, *114*, 7935-7936.
9. Nicolaou, K. C.; Yang, Z.; Shi, G. Q.; Gunzner, J. L., *et al. Nature* **1998**, *392*, 264-269.
10. Nicolaou, K. C.; Frederick, M. O. *Angew. Chem. Int. Ed.* **2007**, *46*, 5278-5282.
11. Murata, M.; Yasumoto, T. *Nat. Prod. Rep.* **2000**, *17*, 293-314.
12. Nicolaou, K. C.; Frederick, M. O.; Burtoloso, A. C. B.; Denton, R. M., *et al. J. Am. Chem. Soc.* **2008**, *130*, 7466-7476.
13. Nicolaou, K. C.; Aversa, R. J.; Jin, J.; Rivas, F. *J. Am. Chem. Soc.* **2010**, *132*, 6855-6861.
14. Nicolaou, K. C.; Gelin, C. F.; Seo, J. H.; Huang, Z. H.; Umezawa, T. *J. Am. Chem. Soc.* **2010**, *132*, 9900-9907.
15. Nicolaou, K. C. *Tetrahedron* **2003**, *59*, 6683-6738.
16. Jas, G.; Kirschning, A. *Chem. Eur. J.* **2003**, *9*, 5708-5723.
17. Baxendale, I. R.; Deeley, J.; Griffiths-Jones, C. M.; Ley, S. V.; Saaby, S., *et al. Chem. Comm.* **2006**, 2566-2568.
18. Hopkin, M. D.; Baxendale, I. R.; Ley, S. V. *Chem. Comm.* **2010**, 2450-2452.
19. Paterson, I.; Findlay, A. D.; Noti, C. *Chem. Comm.* **2008**, 6408-6410.
20. Ley, S. V. *Tetrahedron* **2010**, *66*, 6270-6292.
21. Jessop, P. G.; Heldebrant, D. J.; Li, X. W.; Eckert, C. A.; Liotta, C. L. *Nature* **2005**, *436*, 1102-1102.
22. Jessop, P. G.; Phan, L.; Carrier, A.; Robinson, S.; Durr, C. J.; Harjani, J. R. *Green Chem.* **2010**, *12*, 809-814.
23. Phan, L.; Brown, H.; White, J.; Hodgson, A.; Jessop, P. G. *Green Chem.* **2009**, *11*, 53-59.
24. Mercer, S. M.; Jessop, P. G. *Chemsuschem* **2010**, *3*, 467-470.
25. Ball, P. *Stories of the Invisible: A Guided Tour of Molecules*; Oxford University Press: Oxford, 2001.
26. Zhao, H. Y.; Foss, F. W.; Breslow, R. *J. Am. Chem. Soc.* **2008**, *130*, 12590-+.
27. Walji, A. M.; MacMillan, D. W. C. *Synlett* **2007**, 1477-1489.
28. Simmons, B.; Walji, A. M.; MacMillan, D. W. C. *Angew. Chem. Int. Ed.* **2009**, *48*, 4349-4353.