**SYNSTORIES**

- From Perylene to a 22-Ring Aromatic Hydrocarbon in One Pot

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[4+2] cycloadditions
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- Enantioselective Organocatalytic Michael/Aldol Sequence: Anticancer Natural Product (+)-trans-Dihydrolycoricidine

- Young Career Focus:
  Dr. Alexandre Gagnon (Université du Québec à Montréal, UQÀM, Canada)

- ChemSites: Institute of Transformative Bio-Molecules (ITbM)
  (Nagoya University, Japan)
Dear Readers,

At SYNFORM we don’t wait for the new year for kicking-off a new editorial feature, so in this last issue of 2014 you are about to discover ‘ChemSites’, that highlights chemistry departments, research centers and institutes all over the world. This pilot ChemSites article’s focus is on the Institute of Transformative Bio-Molecules (ITbM), Nagoya University (Japan) and I hope you will find it interesting and informative. I believe ChemSites is an extraordinary vehicle for informing peers, perspectives students and potential postdocs, as well as for raising awareness about the research work and training activities carried out at your institutes and departments. I would like to encourage you to get in touch with me if you wish to have your site featured in a ChemSites article. Clearly, ChemSites is not the only exciting article of this issue, in fact after ChemSites you will have the opportunity to discover how J. McNulty (Canada) came up with the total synthesis of some natural anticancer alkaloids which can be found in tiny amounts in extracts of narcissus and other amaryllidaceae plants. Next, we switch to the chemistry of graphene in order to find out how an international research team led by D. Peña (Spain) managed to produce nanographene structures in a very effective manner. Last but not least, the protagonist of this issue’s Young Career Focus, A. Gagnon (Canada) reveals his scientific interests and some of his future plans.

Enjoy your reading!

Matteo Zanda
Editor of SYNFORM
ChemSites: Institute of Transformative Bio-Molecules (ITbM) (Nagoya University, Japan)

What is the institute’s background and history?

Changing the World with Molecules
The Institute of Transformative Bio-Molecules (ITbM), established in April 2013 at Nagoya University (Japan), aims to create molecules that affect biological systems through extensive collaboration between chemistry and biology. These molecules, which address significant societal issues related to the environment, food production and medical technology, are defined as ‘transformative bio-molecules’, i.e., molecules that can change the world. Led by Center Director Professor Kenichiro Itami of Nagoya University, ITbM merges the strengths of Nagoya University, such as synthetic/catalytic/theoretical chemistry and animal/plant biology to create an interdisciplinary research environment, using molecules as the common language between chemists and biologists. Funded by the Japanese Ministry of Education, Culture, Sports, Science and Technology (MEXT), ITbM is one of nine international research centers selected by the World Premier International Research Center Initiative (WPI) program (http://www.jsps.go.jp/english/e-toplevel/index.html) to advance cutting-edge scientific research by fusing fields and creating new disciplines.

How is the institute structured and organized?
ITbM consists of a young team of 11 Principal Investigators (PIs) with seven Professors from Nagoya University (NU) and four Professors from overseas institutes, who are world-leading researchers in the fields of synthetic chemistry, animal/plant biology and theoretical science. Synthetic chemists, Professors Kenichiro Itami (NU; Center Director), Shigehiro Yamaguchi (NU; Vice-Director), Takashi Ooi (NU), Cathleen M. Crudden (Queen’s University, Canada) and Jeffrey W. Bode (ETH Zurich, Switzerland) collaborate extensively with plant biologists Professors Tetsuya Higashiyama (NU; Vice-Director), Toshinori Kinoshita (NU), and Keiko Torii (University of Washington, USA), animal biologists Professors Takashi Yoshimura (NU) and Steve A. Kay (University of Southern California, USA) along with theoretical scientist

Figure 1 ITbM’s main research fields

Figure 2 ITbM’s 11 PIs and 4 Co-PIs
Professor Stephan Irle (NU) to develop molecules that enable us to ‘understand’, ‘see’ and ‘regulate’ living organisms. ITbM has adopted a Cooperative-PI (Co-PI) system for overseas PIs where the Co-PIs conduct the research at ITbM whilst the overseas PIs are at their host institute. The labs at ITbM are organized in a ‘Mix-Lab’ fashion, where chemists, biologists and theoreticians work side by side in the lab, which breaks the conventional barriers between research groups/fields, and enables interactive discussions on a daily basis to promote interdisciplinary research.

ITbM’s new building is to be finished in spring 2015, and will reflect the ‘Mix-Lab’ concept throughout.

The institute has three sub-centers that support ITbM’s interdisciplinary research:
(i) Molecular Structure Center with analytical devices to analyze the structure of molecules;
(ii) Chemical Library Center to create a databank of synthesized/commercial molecules for bioassay studies; and
(iii) Live-Imaging Center with leading-edge laser microscopes to enable bio-imaging of molecules in live cells.

These sub-centers are equipped with the latest measurement/analysis techniques managed by specialized staff.

Many of the postdoctoral researchers at ITbM are from overseas and the institute has English/Japanese-speaking administrative staff members, who organize international symposia, build global networks and provide local support for daily life including housing, medical care and children’s education – all aimed at making sure the overseas researchers are comfortable living and carrying out research in Nagoya.

ITbM has partnerships with overseas institutions, including the overseas PI’s host institutes, ETH Zurich, Queen’s University, the University of Washington and the University of Southern California. In addition, ITbM is working closely with the National Science Foundation’s Center for Selective C–H Functionalization (Center Director: Professor Huw Davies, Emory University, USA) (http://www.nsf-cchf.com), which brings together leading experts in a range of chemical disciplines, by carrying out collaborative projects through active exchange of personnel (students/researchers/faculty) and ideas between the institutions.

What are the institute’s research focus and scientific aims?

ITbM’s main research focus is to develop new catalysts and reaction systems in order to generate molecules that enable visualization of biological activities and control of biological systems, such as molecules that dramatically enhance plant growth and improve animal reproduction.

The four core projects running at ITbM are the development of: (i) molecule-controlled plant reproduction; (ii) molecular tools to combat the parasitic Striga plant issue in agriculture; (iii) molecular control of circadian rhythm in animals; and (iv) molecular innovation for bio-imaging and bio-sensing. Each project is based on the collaboration between chemistry and biology to deliver bio-molecules that can have significant societal impact.

ITbM also has an internal grant system, known as the ITbM Research Award, where young researchers from different disciplines have the opportunity to make their original research proposals in order to accelerate interdisciplinary research. Through the ‘Mix-Lab’ system, synthetic chemists, animal/plant biologists and theoreticians work in the same
Center Director Professor Kenichiro Itami’s message

“Molecules are small but are essential to all life on earth. It is my strong belief that molecules have the power to change the way we do science and the way we live. The main target of ITbM is to develop transformative bio-molecules that will be the key to solving urgent problems at the interface of chemistry and biology. The identity of ITbM is its capability to develop completely new bioactive molecules with carefully designed functions. With biologists knowing what functions they need in molecules and chemists knowing how to install these functions, we hope to make unprecedented scientific advances at ITbM. We are looking forward to working with ambitious researchers worldwide and nurturing the next generation of cutting-edge research, unrestricted by the bounds of traditional disciplines. Located in central Japan, Nagoya University’s ITbM provides an enthusiastic research environment for people from all over the world wanting to connect molecules, create value, and change the world.”

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The group of Professor James McNulty at McMaster University in Hamilton (Ontario, Canada) has recently reported a short, asymmetric total synthesis of the anticancer amaryllidaceae alkaloid (+)-trans-dihydronarciclasine (3). “The amaryllidaceae plant family, which includes well-known species such as daffodils, jonquils and snowdrops, has been of medicinal interest for millennia,” explained Professor McNulty. “Extracts of narcissus and pancratium were employed by ancient Greek (Theophrastus) and Roman (Pliny) physicians in the treatment of skin cancers and other ailments. The modern-era isolation of alkaloids from amaryllidaceae plants began in the mid-19th century with the structure of bases such as lycorine being firmly established by the late 1950s,” he added. Interest in the lycorane class of amaryllidaceae natural products increased with the discovery of new members demonstrating potent nanomolar anticancer activity, notably narciclasine (1) (G. Ceriotti *Nature* 1967, 213, 595), pancratistatin (2) (G. R. Pettit et al. *Chem. Commun.* 1984, 1693; *J. Nat. Prod.* 1984, 47, 1018) and trans-dihydrolycoricidine (3) (G. R. Pettit et al. *J. Nat. Prod.* 1993, 56, 1682). Interest in the isolation, structure, biosynthesis, total synthesis and biological evaluation of amaryllidaceae constituents continues unabated (Z. Jin *Nat. Prod. Rep.* 2013, 30, 849).

Professor McNulty has been investigating various aspects of the chemistry of these constituents for the last 18 years. “I was conducting bioassay-guided isolation on unrelated marine-sponge-derived natural product extracts as a postdoctoral fellow in Bob Pettit’s group at ASU,” explained Professor McNulty. “Two of my colleagues, Drs. Brian Orr and Noleen Melody, were preparing synthetic derivatives of pancratistatin (1) and the anticancer activity of some of them was quite astonishing.” According to Professor McNulty, of equal surprise was the fact that nothing was known regarding the mechanism of action of these anticancer agents, meaning that a novel biological target might be involved. “Analysis using the COMPARE algorithm demonstrated no correlation of activity of these compounds with any known class of anticancer agent! As an Assistant Professor, this was one of the

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**Figure 1**

narciclasine (1)  
pancratistatin (2)  
(+)-trans-dihydrolycoricidine (3)
first projects we got off the ground,” continued Professor McNulty. To date, the group has prepared the core lycorane structure employing four totally different synthetic strategies as well as the synthesis of fully functionalized seco-analogues. Through extensive synthetic and biological evaluations, the minimum anticancer pharmacophore in the lycorane series was determined to be that contained within trans-dihydrolycoricidine (3) (T. Hudlicky et al., *Bioorg. Med. Chem. Lett.* 2004, 14, 2911; J. McNulty et al., *Bioorg. Med. Chem. Lett.* 2005, 15, 5315). Further deletions or stereochemical modifications to 3 result in compounds with significantly reduced, or no, anticancer activity, conferring a privileged standing on natural product 3 as a target for total synthesis.

The total asymmetric synthesis of trans-dihydrolycoricidine (3) was achieved in only nine chemical steps from azidoacetone (5) and the methylenedioxy-substituted cinnamaldehyde 4 shown in Scheme 1. While a few examples of organocatalytic [3+3] Michael–aldol sequences have been reported, some of which utilize a doubly activated methylene to control regioselectivity, no prior report on the use of an
α-nitrogen-substituted ketone existed in the literature. The authors' current view on the mechanism of the stepwise cycloaddition reaction is that it proceeds via iminium ion activation. “We were delighted to find that azidoacetone reacts exclusively at the azidomethylene (α'), adding to the iminium ion generated from the alkenal and chiral secondary amine 6,” said Professor McNulty. “The subsequent intramolecular aldol reaction is not spontaneous and requires addition of a second tertiary base, such as quinidine (8). The absolute stereochemistry of the process is controlled only by the chiral prolinol silyl ether catalyst to give the major stereoisomer shown (9).”

With the key cyclohexane ring in place, the target was prepared in eight further steps as outlined in Scheme 2.

“The synthesis of the polyhydroxy-containing lycorane core structure has been a lucrative proving ground for the development of synthetic methodology and a fantastic training ground for students in synthetic organic chemistry over the years,” explained Professor McNulty. “In addition to issues of regio- and stereocontrol, there are several pitfalls and opportunities for elimination reactions and aromatization of the polyhydroxyl ring that need to be successfully navigated.” In addition to completion of the synthesis of 3, Professor McNulty noted that the general methodology outlined in Scheme 1 opens up an asymmetric entry to aminocyclitols in general, which are an important subclass of natural and non-natural compounds of wide-ranging therapeutic potential. “The methodology allows construction of the natural product 3 and many structural analogues including epimeric and deoxy derivatives. We have been able to explore the biological activity of these compounds and uncover new insights into the pharmacophore as well as target and mechanism of action, studies that will be reported in the near future,” concluded Professor McNulty.

**About the authors**

**James McNulty** was born in Glasgow, Scotland (UK). He received B.Sc., M.Sc. and Ph.D. degrees at the University of Toronto (Canada) with Professor Ian Still (1993). He subsequently completed postdoctoral work at the University of Geneva (Switzerland) under the guidance of Professor Charles Jefford and at Arizona State University in Tempe, Arizona (USA) under the guidance of Professor Bob Pettit. He began his independent career at Brock University (Canada), moving to McMaster University (Canada) in 2003 where he is now Full Professor. His research focuses on methodology development in olefination chemistry, late-transition-metal and organocatalysis, as well as applications in various areas of total synthesis and chemical biology.

**Carlos Zepeda-Velazquez** completed his B.Sc. degree in pharmaceutical chemistry from La Salle University (USA) and his M.Sc. in organic chemistry from National Autonomous University of Mexico in 2003 and 2006, respectively. Subsequently, he worked as a process chemist at Signa, S.A de C.V. (Mexico) where he focused on the development and manufacture of chemical reagents that are used as raw materials in the pharmaceutical industry. For his doctoral studies he moved to Canada in 2009 and joined the group of Professor McNulty at McMaster University, where he developed an enantioselective synthesis of trans-dihydrolycoricidine. Currently he is undertaking postdoctoral studies at the Ontario Institute of Cancer Research (Canada) under the supervision of Dr. Rima Al-Awar, contributing to the design, synthesis and evaluation of novel anti-tumor agents.

**Matteo Zanda**
The chemistry of graphene is attracting enormous interest owing to the exceptional properties of this material. Recently, a collaboration between chemists at Centro de Investigación en Química Biolóxica e Materiais Moleculares (CIQUS, University of Santiago de Compostela, Spain) and physicists from IBM Research – Zurich (Switzerland) resulted in the discovery of a novel synthetic approach to graphene fragments, which may be used for the fabrication of electronic devices. The graphene templates were subsequently characterized by atomic force microscopy (AFM). The research team from CIQUS, which included Professors Diego Peña, Enrique Gutián and Dolores Pérez, and PhD student Sara Collazos, developed the synthetic methodology to obtain nanographenes by chemical methods in solution, while the IBM team, which involved Drs. Leo Gross and Gerhard Meyer, and PhD student Bruno Schuler, characterized these molecules by AFM. The research was coordinated by Professor Peña (CIQUS) and Dr. Gross (IBM). Both groups are partners in the Large European Project PAMS (http://pams-project.eu/), Planar Atomic and Molecular Scale Devices, whose main objective is the development, fabrication and characterization of planar atomic and molecular scale electronic devices.

Professor Peña said: “Graphene is considered a unique material, which is leading to the emergence of a completely new technology. One of the biggest challenges in this new field is the development of methodologies for the preparation of this material with nanometric size and high quality: if we can gain perfect control over their size and geometry, then we could explore new applications for high-performance electronic devices.” The method reported in this paper allows well-defined nanographenes to be obtained in one pot from perylene, a very common organic compound. The preparation of these materials with different shapes and sizes could be crucial for building graphene-based electronic circuits, molecular machinery and/or single molecule electronic devices.

Professor Peña explained: “This method is based on the reactivity of arynes, which can act as a ‘molecular glue’ to paste graphene fragments together. In particular, we employed two sequential cycloaddition reactions involving arynes: a Diels–Alder reaction on the bay region of perylene, followed by a Pd-catalyzed cyclotrimerization. Since the clover-shaped nanographenes obtained in this transformation were extremely insoluble, characterization by classical methods (e.g. NMR) was not an option, so we proposed that our colleagues in IBM should attempt the identification by atomic-resolved AFM. Notably, besides the characterization of the anticipated graphene molecule they were able to detect some unexpected and interesting byproducts.”

Dr. Gross continued: “We achieved the first atomic-resolved atomic force microscopy (AFM) images of molecules in 2009. The key was the termination of the scanning probe tip by a single CO molecule. Soon after, we tried to make use of that technique for molecular structure identification and we also refined the technique to increase the information that can be obtained.”

Using AFM, the authors identified natural products that could not be solved using standard techniques such as mass spectrometry and nuclear magnetic resonance alone. They also obtained additional information by AFM, including the exact adsorption geometry of molecules, information about the bond order of individual bonds within molecules, the charge distribution within molecules, some information related to element specificity and identification of byproducts.

Dr. Gross concluded: “In terms of a wider applicability of AFM for structure identification, one challenge is to expand...
the classes of molecules that can be studied. The recent case, namely a 22-ring aromatic molecule, was the largest molecule that we have been able to resolve so far. However, with this molecule we reached about the size of molecules that can be thermally evaporated. A challenge for the future is to switch to other preparation methods, for example, electrospray deposition, that would allow us to deposit even larger molecules without breaking them."

Matteo Zanda

Figure 2 Atomic force microscopy (AFM) image of a clover-shaped nanographene (Credit: Bruno Schuler, IBM)
About the authors

Diego Peña Gil was born in Santiago de Compostela (Spain) in 1974. He graduated in Chemistry at the University of Santiago de Compostela in 1998, where he also obtained his PhD under the guidance of Professors Enrique Guitián and Dolores Pérez, working on transition-metal-catalyzed cycloaddition reactions of arynes (2001, Special Doctorate Award). He spent short predoctoral stays in the groups of Professors Eric N. Jacobsen (1999, Harvard University, USA), Paul Knochel (2000, LMU, Munich, Germany) and Antonio M. Echavarren (2001, UAM, Madrid, Spain). During 2002 and 2003 he joined the group of Ben L. Feringa (Groningen University, The Netherlands) as a Marie Curie Postdoctoral Fellow working on asymmetric catalysis, with short research stays in the group of Johannes G. de Vries (DSM, Geleen, The Netherlands). In 2004 he returned to the University of Santiago de Compostela as Ramón y Cajal researcher, where he has been Associate Professor since 2008. His main research interests are focused on the development of new synthetic methodologies, metal-based homogeneous catalysis, the chemistry of organic intermediates such as arynes, the synthesis of nano-sized polycyclic aromatic compounds and nanographenes, and their study as new molecular materials.

Sara Collazos Suárez was born in Pontevedra (Spain) in 1987. She graduated in Chemistry at the University of Santiago de Compostela (Spain) in 2010, where she is working as PhD student on the synthesis of large aromatic compounds and nanographenes.

Dolores Pérez Meirás was born in Ferrol (A Coruña, Spain). She graduated (with honors) in Chemistry at the University of Santiago de Compostela (Spain), where she also carried out her graduate studies under Professors Luis Castedo and Enrique Guitián. After obtaining her PhD in 1991, she did a two-year postdoctoral stay as a Fulbright Fellow at the University of California at Berkeley (USA) in the group of Professor K. Peter C. Vollhardt, and a shorter stay in the group of Professor Stephen L. Buchwald at the Massachusetts Institute of Technology (USA). In 1995 she joined the Faculty of the University of Santiago de Compostela as Assistant Professor and since 2000 she has been Associate Professor of Organic Chemistry. Her main research interests are the discovery of new metal-catalyzed reactions of synthetic interest, the development of aryne chemistry and, in particular, its application to the synthesis of complex polycyclic aromatic systems of interest in the field of materials science. She is the Deputy Director of the Centre for Research in Biological Chemistry and Molecular Materials (CIQUS) at the University of Santiago de Compostela.

Enrique Guitián Rivera received his PhD from the University of Santiago de Compostela (Spain) in 1981 for work in the field of natural product synthesis under Professor Luis Castedo. After a postdoctoral stay at the University of Hannover (Germany) under Professor Ekkehard Winterfeldt, he continued his career at Santiago (Associate Professor, 1985–1992; Full Professor, 1992). His main research interests lie in the fields of natural product synthesis and aryne chemistry, especially pericyclic and transition-metal-catalyzed reactions of arynes.

Bruno Schuler is working as a PhD student at IBM Research – Zurich Laboratory (Switzerland). The main focus of his work is molecular structure determination using atomic force microscopy. In 2011, he joined the IBM Research – Zurich Laboratory and the group of Gerhard Meyer for his Masters’ thesis. He obtained...
his Masters and Bachelor degrees from ETH Zurich (Switzerland).

**Leo Gross**, a native of Berlin (Germany), has been a research staff member at the IBM Research – Zurich Laboratory since 2009. He is working on atomic/molecular manipulation by scanning tunneling microscopy (STM) and atomic force microscopy (AFM), and on nanostencil lithography. He has been with the IBM Research – Zurich Laboratory since 2005, having originally joined IBM Research as a postdoctoral fellow in the group of Gerhard Meyer. Leo Gross received his PhD in Physics in 2005 from the Free University of Berlin (Germany) in the group of Professor Karl-Heinz Rieder and the Master’s (Diploma) degree in Physics in 2001 from the University of Muenster (Germany) in the group of Professor Harald Fuchs. He received the Feynman Prize for Experiment in 2012 and the Gerhard Ertl Young Investigator Award in 2010.

**Gerhard Meyer** is research staff member in the ‘Physics of Nanoscale Systems’ group at the IBM Research – Zurich Laboratory. His main research interests are in the area of scanning probe microscopy and epitaxial growth, in particular low-temperature scanning tunneling microscopy and atomic force microscopy, atomic/molecular manipulation and studies on the growth of/on ultrathin insulating films. He received his PhD from the University of Hannover (Germany) in 1987. Following a postdoctoral fellowship at the IBM Research Laboratory in Yorktown Heights (USA) he joined the group of Prof. Karl-Heinz Rieder at the Free University Berlin, starting a project on low-temperature scanning probe microscopy. In 2000 he became staff member of the Paul Drude Institut für Festkörperelektronik, Berlin (Germany) until 2002 when he moved to the IBM Research – Zurich Laboratory. For his work in scanning probe microscopy he received several IBM awards including an IBM Corporate Award, the German Nano-Science Prize (2002) and the Robert Wichard Pohl Prize of the German Physical Society (2011). Since 2009, he has been Fellow of the American Physical Society. In 2012 he received the Feynman Prize for Experiment. He has published more than 120 publications and presented more than 100 invited talks in the area of surface science and nanoscience. His research projects have been supported by several national and EU projects fostering international collaborations and recently, in 2011, he was awarded an ERC advanced grant.
Background and Purpose. SYNFORM will from time to time meet young up-and-coming researchers who are performing exceptionally well in the arena of organic chemistry and related fields of research, in order to introduce them to the readership. This SYNSTORY with a Young Career Focus presents Dr. Alexandre Gagnon (Université du Québec à Montréal, UQÀM, Canada).

INTERVIEW

SYNFORM | What is the focus of your current research activity?

Dr. A. Gagnon | My research activities are focusing on two fields: organic and medicinal chemistry. Our first research theme is centered around the development of metal-catalyzed reactions that involve organobismuthanes and that allow the introduction of highly functionalized fragments on medicinally relevant scaffolds. Our second research program deals with the preparation of modulators of epigenetic targets such as the DNA methyltransferases (named DNMTs). Epigenetics is an exciting field which studies the changes that occur on chromosomes without affecting the DNA sequence. Although this field is still in its infancy, the involvement of enzymes that perform epigenetic modifications in the development of numerous diseases is becoming clearer. Unfortunately, very few compounds that can modulate the activity of epigenetic enzymes are known, justifying research activities in that field.

SYNFORM | When did you get interested in synthesis?

Dr. A. Gagnon | Chemistry was not my favorite subject in high school. Back then, I was more interested in mathematics and physics. My interest for this topic surfaced when I took an organic chemistry class in college given by Roger Gauthier. I was particularly attracted by the rational aspect of this science and the possibility of transforming molecules by breaking and forming new bonds. My passion for organic chemistry grew even further when I attended a course given by Professor André Charette during my first year as an NSERC student. In 1996, he joined the group of Professor André B. Charette as an NSERC graduate awardee to begin his doctoral work on the development of metallo-cyclopropanation reactions involving an unprecedented gem-dizinc carbenoid reagent. In 2001, after obtaining his Ph.D., he moved to New York, NY (USA) as an NSERC post-doctoral fellow to work on the total synthesis of xestocyclamine A under the supervision of Professor Samuel J. Danishefsky. In 2003, he started his industrial career at Boehringer Ingelheim in Laval (Canada) as a research scientist, working on the development of inhibitors of viral targets for the treatment of HIV and HCV. While at Boehringer Ingelheim, he also published numerous papers on the use of tricyclopropylbismuth as a cyclopropyl transfer agent. In 2010, he returned to the USA and joined Constellation Pharmaceuticals in Cambridge, MA, as a senior research scientist to perform research on the development of modulators of epigenetic targets. In 2011, Dr. Gagnon began his independent academic career in the chemistry department of UQÀM. His research interests lie at the interface of organic, organometallic, and medicinal chemistries. His work focuses on the development of metal-catalyzed reactions for the preparation of bioactive compounds and on the synthesis of modulators of epigenetic enzymes. He has authored more than 30 papers, trained more than 30 students and is an inventor on eight patents. His research programs are funded by the Fonds de Recherche du Québec, Nature et Technologies (FRQNT), the Natural Sciences and Engineering Research Council of Canada (NSERC), and the Canada Foundation for Innovation (CFI). He is a member of Pharmaqam and the Centre in Green Chemistry and Catalysis (GGCC) and is a member of the executive committee of the Fondation Lucien Piché.
undergraduate student at the Université de Montréal. André was an exceptional teacher who knew how to communicate his knowledge of chemistry and his enthusiasm for science. Also, Professor Davit Zargarian, with whom I did one summer research term, was a very inspirational mentor who taught me a lot in research and who gave me an interest for organometallic chemistry. I was also extremely privileged to learn from Professor Samuel J. Danishefsky during my post-doctoral appointment and from many spectacular scientists in the industry, such as Jean-Christophe Harmange and Brian Albrecht at Constellation Pharma and Michael Bös and Paul Anderson at Boehringer Ingelheim. These are all exceptional people who had a tremendous influence on my scientific development over the years and who fuelled my desire to pursue a career in chemistry.

**SYNFORM | What do you think about the modern role and prospects of organic synthesis?**

**Dr. A. Gagnon** | Organic chemistry has suffered dramatically from the hurdles that the pharmaceutical industry has been facing over the past decade. As a consequence, it has become very difficult to convince the younger generation to pursue a career in this discipline. However, I firmly believe that organic chemistry is still an extremely important science that will play a major role in solving the problems that our society is and will be facing in the future. I think that we will continue to see a strong involvement of organic chemistry in many other scientific fields such as materials science, biology, medicinal chemistry and biopharmaceutical sciences. I also believe that the pendulum will swing back in the pharmaceutical industry and that there will be a larger need

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**Scheme 1**

**Alkylbismuthanes**

![Scheme 1](image_url)

**Arylbismuthanes**

![Scheme 1](image_url)

**FG = Functional Group**
for highly competent organic chemists. In fact, we should expect a strong demand for more efficient drugs to treat diseases associated with the aging of the population. Thus, I believe that there will always be jobs for highly talented and well-trained chemists who are passionate about organic chemistry.

SYNFORM | Your research group is active in the area of medicinal chemistry and development of new synthetic methodology. Could you tell us more about your research and its aims?

Dr. A. Gagnon | On the medicinal chemistry front, we are collaborating with experts in academia and industry to develop modulators of various epigenetic targets.¹ As a synthetic chemistry group, we are responsible for the preparation of the molecules whereas our collaborators are taking care of the determination of their biological activities. Currently, we are mainly focusing on the synthesis of non-nucleoside inhibitors of DNMTs because the marketed drugs that target these enzymes possess a nucleoside core and thus have poor pharmacokinetic profiles. On the methodology development front, we are working on a concept that we called functional group manipulation to prepare highly functionalized organometallic reagents containing a carbon–bismuth bond. These reagents are very interesting because they are easy to prepare and because they show remarkable functional group tolerance. In addition, their reactivity depends on the oxidation state of the bismuth center, with pentavalent reagents behaving as electrophiles and trivalent counterparts reacting as nucleophiles. Using this diametrically opposite reactivity, our group has reported a portfolio of methodologies involving these reagents for the construction of C–C, C–N, and C–O bonds.²

SYNFORM | What is your most important scientific achievement to date and why?

Dr. A. Gagnon | Having spent close to ten years in the industry and only three years in academia, I believe (and I hope!) that my most important achievements lie ahead of me. However, if I were to pick one contribution to the field, I would choose the N-cyclopropylation reaction of azoles and amides involving tricyclopropylbismuth.³ This method was the first to allow the direct transfer of a cyclopropyl group (a unit which is particularly important in medicinal chemistry) on these substrates.

REFERENCES
