NEW *N*-HYDROXYPHTHALIMIDES FOR AEROBIC OXIDATION

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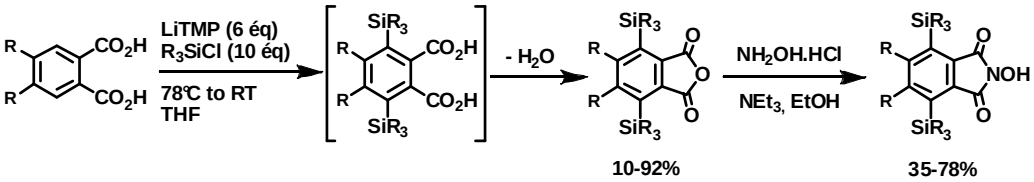
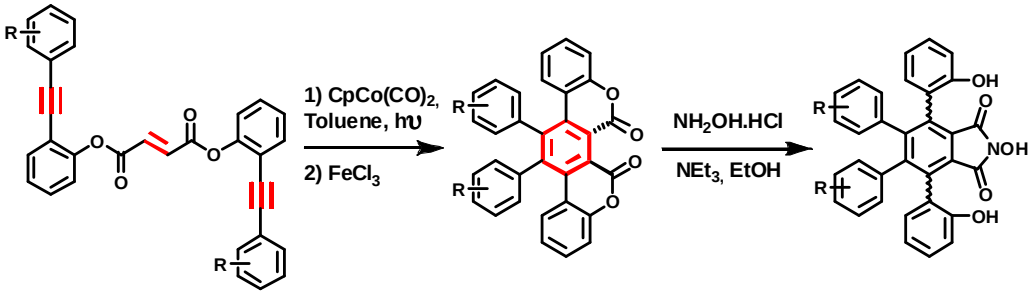
Aerobic oxidation using *N*-hydroxyphthalimides (NHPI) currently founds its main interests in the use of environment-friendly catalysts under mild conditions.[1] However, the use of large amounts of catalyst (typically 10 mol%) calls for the synthesis of more active NHPI analogs. We herein present two new synthetic routes to highly substituted analogs and their potency in catalysis.

Bringing steric hindrance around the active site was thought to be helpful for improving the active species stability. We developed a bis-*ortho*-metalation/silylation of unprotected phthalic acids, using LiTMP as base, and chlorotrialkylsilane as in-situ electrophile. After dehydration, bis-*ortho*-silylated phthalic anhydrides are obtained. Straightforward conversion to *N*-hydroxyimides afforded new catalysts with promising properties.[2]



To date, *N*-hydroxytetraphenylphthalimide (NHTPPI) analogs are the most active catalysts,[3] but their access remain difficult. An intramolecular [2+2+2] cyclotrimerisation of an ene-diyne has been developed, affording an undescribed pentacyclic phthalic bis-lactone skeleton, which contains the built-in tetra-arylated central ring. The complete route from commercial starting materials to phenol-containing NHTPPI analogs is described, as well as the methodology limitations. As the final products present atropisomerism and C_2-symmetry, chiral catalysts may be obtained, leading to enantioselective aerobic oxidation.[4]



References :

1. Recupero, F.; Punta, C. *Chem. Rev.* **2007**, *107*, 3800–3842.
2. Michaux J., Bessieres B., Einhorn J. *Tetrahedron Letters* **2012**, *53*, 48-50.
3. Nechab, M.; Einhorn, C.; Einhorn, J. *Chem. Commun.* **2004**, 1500-1501.
4. Nechab, M.; Kumar, D.N.; Philouze, C.; Einhorn, C.; Einhorn, J. *Angew. Chem. Int. Ed.* **2007**, *46*, 3080–3083.

DESIGN AND SYNTHESIS OF NOVEL WATER-SOLUBLE PROSTHETIC GROUPS FOR 18F LABELING OF PEPTIDES AND PROTEINS

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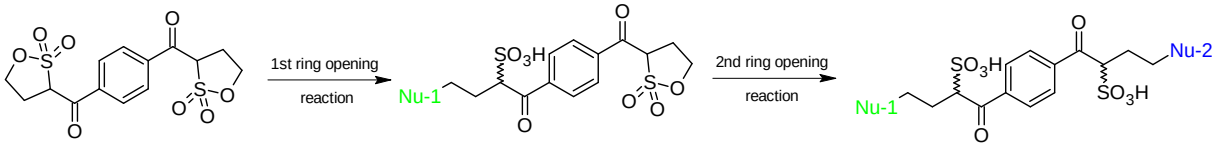
Positron Emission Tomography (PET) is a noninvasive imaging technique based on the use of radionuclides that are incorporated into more or less complicated molecules having a specific biological activity. That radiolabelled biological tool after ingestion will lead to information on cell physiology and function of organs. In the context of PET, high molecular weight complex bioactive chemical structures, such as peptides, proteins and oligonucleotides are increasingly proposed as radiopharmaceuticals and their applications appear very promising in the field of nuclear medicine and oncology.

Fluorine 18 is the radionuclide that offers the best characteristics for optimal imaging study [1] (optimal half-life of ~110 min, higher resolution, pseudo-isostere of hydrogen, isostere of oxygen). In the literature, 18F-labeling of peptides or macromolecules is classically performed through the use of a prosthetic group carrying the radioisotope [2]. This approach involves the preparation of the so functionalized and radiolabeled prosthetic group, followed by its chemo-selective conjugation with a reactive function of the peptide or protein. Introduction of fluorine-18 at the latest stage of the prosthetic group synthesis and automation of the whole process including radiolabelling of a biological molecule remain two main challenges of the field.

In our work, we developed a homobifunctional cross-linker based on a bis-sultone benzenic scaffold [3]. The potential utility of this bioconjugation reagent was demonstrated through the preparation of an original prosthetic group for the [^{18}F]-labelling of a biological relevant peptide. The labeling strategy is based on the nucleophilic fluorination via the ring-opening of a first sultone moiety followed by the nucleophilic ring-opening of the second remanent sultone by a reactive amine or thiol function of a biomolecule (Cf. scheme below).



Nu-1 & Nu-2 = X^-, R-NH_2, R-OH, R-SH or alpha-nucleophile

Beyond the one-step radiolabelling of the peptide, the second main advantage of this strategy is the release of free sulfonic acid moieties making the separation of the targeted [^{18}F]-tagged sulfonated compound from its non-sulfonated precursor easier and thus faster. That simple strategy was efficiently automated on a GMP Tracerlab Mx module allowing the handling of much higher amounts of radioactivity.

[1] Ametamey, S. M.; Honer, M.; Schubiger, P. A. *Chem. Rev.* **2008**, *108*, 1501

[2] Wester, H. J.; Schottelius, M. in *PET Chemistry: The Driving Force in Molecular Imaging*, **2007**, vol. 62, p. 79

[3] Priem, T.; Bouteiller, C.; Camporese, D.; Romieu, A.; Renard, P.Y. *Org. Biomol. Chem.* **2012**, *10*, 1068

FURFURAL: A GREEN AND RENEWABLE PRECURSOR TOWARDS SUBSTITUTED AROMATIC COMPOUNDS

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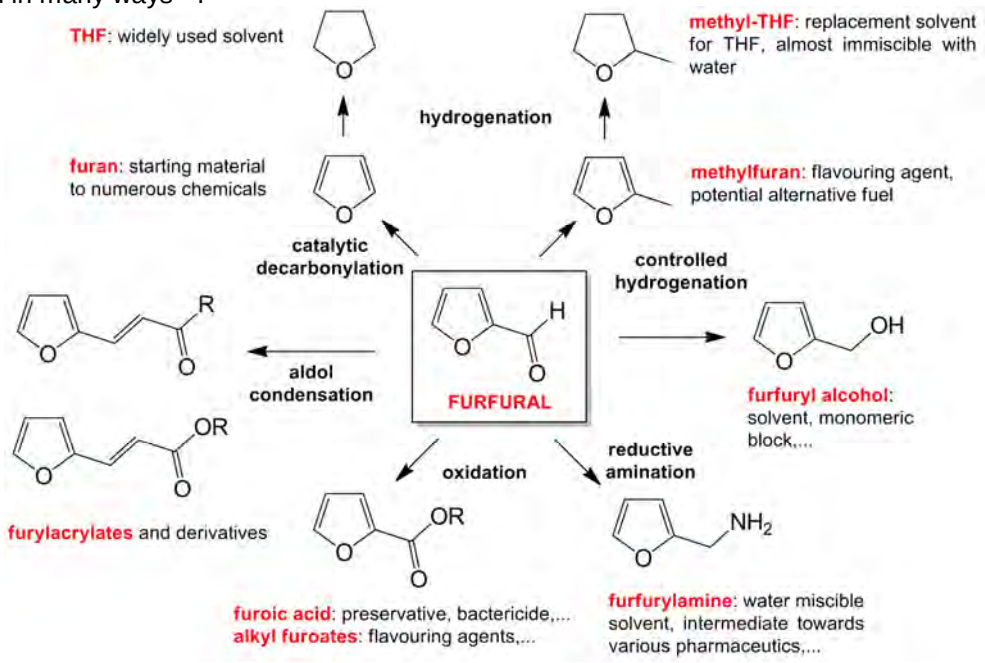
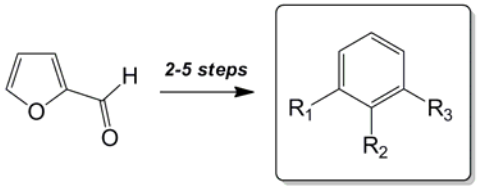
Furfural (from latin *furfur*) is a natural compound derived from C5 saccharides that can be extracted from corn or sugarcane wastes, which are usually not used in any way. As such, the use of furfural as starting material towards other scaffolds of interest is a very attractive perspective, and it has been illustrated in many ways[1,2].



Schema 1

To the best of our knowledge, not many investigations have been carried out to extend the usefulness of the furfural as precursor to other systems, such as substituted benzene rings. Yet this would represent a renewable alternative to existing routes that mostly involve reactants coming from petroleum.



Schema 2

We will exemplify in this presentation our recent yet unpublished work in this field.

1 Gallezot, P. *Chem. Soc. Rev.* **2012**, *41*, 1538-1558.

2 Stevens, J.G., Bourne, R.A., Twigg, M.V., Poliakoff, M. *Angew. Chem. Int. Ed.* **2010**, *49*, 8856-8859.

CHEMISTRY AT BAYER CROPSCIENCE : INNOVATION FROM CONCEPT TO PROCESS

D. Bernier, and all Disease Control research scientists at Bayer CropScience

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Many factors (such as increasing world population by near-to-constant arable area, changing food habits, increasing demand for alternative energies such as biofuels, and climatic changes) will impact the delicate balance between agricultural supply and demand in the near future.
To provide an answer to these changes, key players in crop protection must provide innovative solutions to improve crop yields.
At Bayer CropScience, chemical technologies are seen as a centerpiece of this innovation process, from the discovery of new active ingredients to the development and production of commercial products.

Taking fungicidal research as an example, natural products (e.g. Pterulone A, (-)-Pironetin, Cinnabaramide A and Belactosins) will be shown to constantly provide highly valuable inspiration for innovative chemistry in crop protection. This highly rewarding but synthetically challenging approach will be shown to require strong partnering with key experts worldwide.

Finally, the importance of chemical technologies (such as laboratory automation or process research) in supporting discovery and production of new active ingredients and securing IP rights will be discussed, to provide a view of how chemical research within Bayer CropScience contributes to fulfilling tomorrow's societal needs.

Thursday Afternoon

MELLAL Dénia

Synthesis of aminoacyl-tRNA bisubstrate analogue, for the study and the inhibition of FemX transferases

DARDENNE Jérémy

Pharmacomodulation de la meiogynine A, une molecule d'origine naturelle agissant sur les proteines de l'apoptose

LENORMAND Hugo

New spirosilanes as fluoride sensors

CATANA Dan-Andrei

Torsion angles modulation of dinucleotides using a phostone modification

BENSOUSSAN Charlélie

Efforts towards the synthesis of the fragment C_{30}-C_{52} of amphidinol 3

HUANG Min

Studies on the mechanism of glycosylation reactions. Determination of primary ^{13}C kinetic isotop effects at naturel abundance using high field NMR methods

GIROS Audrey

Original disilanes as intermediates for the synthesis of 10-silatestosterone

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Dr. MAGNIER Emmanuel

How can we introduce a perfluorinated group in an electrophilic fashion?

SYNTHESIS OF AMINOACYL- tRNA BI-SUBSTRATE ANALOGUE, FOR THE STUDY AND THE INHIBITION OF FemX TRANSFERASES

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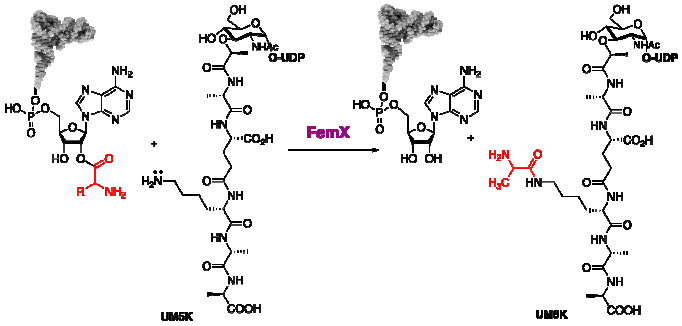
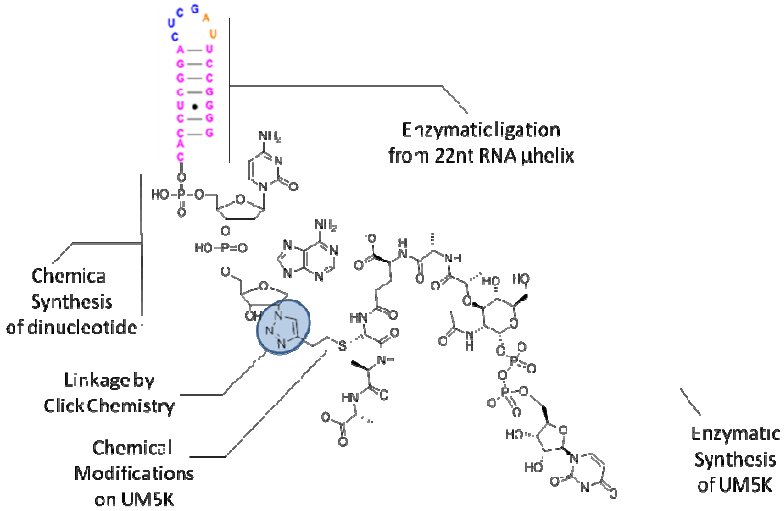
UPMC – Institut Parisien de Chimie Moléculaire
Equipe Glycochimie Organique Biologique et Supramoléculaire
UMR CNRS 7201, 4 place Jussieu 75252 Paris Cedex 05

The tRNA-dependent aminoacyl Fem transferases catalyze an essential step of peptidoglycan synthesis in pathogenic bacteria and are considered as attractive target for the development of novel antibiotics. FemX of *Weissella Viridescens* **FemXwv**, the model enzyme of this family, transfers L-Ala from Ala-tRNA to the ε-amino group of L-Lys in the peptidoglycan precursor UDP-MurNAc-pentapeptide **UM5K** (Scheme A).[1, 2, 3]



Scheme A: Postulated catalytic mechanism of FemX



Scheme B: aa-tRNA bi-substrate analogue

Recently, we designed the semi-synthesis of a highly modified aminoacyl-tRNA bi-substrate analogue, included the replacement of the ester bond by a triazole ring to connect the two substrates of **FemXwv**: the **tRNA** and the **UM5K** (Scheme B). This oligonucleotide has been tested as inhibitor of **FemXwv** to explore the catalytic mechanism of this enzyme. This assay was a success and revealed a low IC_{50} value of 0.8nM *(manuscript in preparation).*

Financial support : Île de France

References

[1.] M. Fonvielle, M. Chemama, R.Villet, M. Lecerf, A. Bouhss, J-M. Valéry, M. Ethève-Quelquejeu, M. Arthur, *Nucleic Acids Res*., **2009**, *Vol. 37*, No. 5, 1589-1601 ; [2.] M. Fonvielle, M. Chemama, M. Lecerf, R. Villet, P. Busca, A. Bouhss, M. Etheve-Quelquejeu, M. Arthur *Angew.Chem. Int .Ed.* **2010**, *49*, 5115-5119 ; [3.] M. Chemama, M. Fonvielle, M. Lecerf, D. Mellal, H. Fief, M. Arthur, M. Ethève-Quelquejeu, *Current Protocols in Nucleic Acid Chemistry,* **2011**, chapt. 4, Unit 4.44.

PHARMACOMODULATION DE LA MEIOGYNINE A, UNE MOLECULE D'ORIGINE NATURELLE AGISSANT SUR LES PROTEINES DE L'APOPTOSE

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Anaïs Pujals (2), Joëlle Wiels (2)

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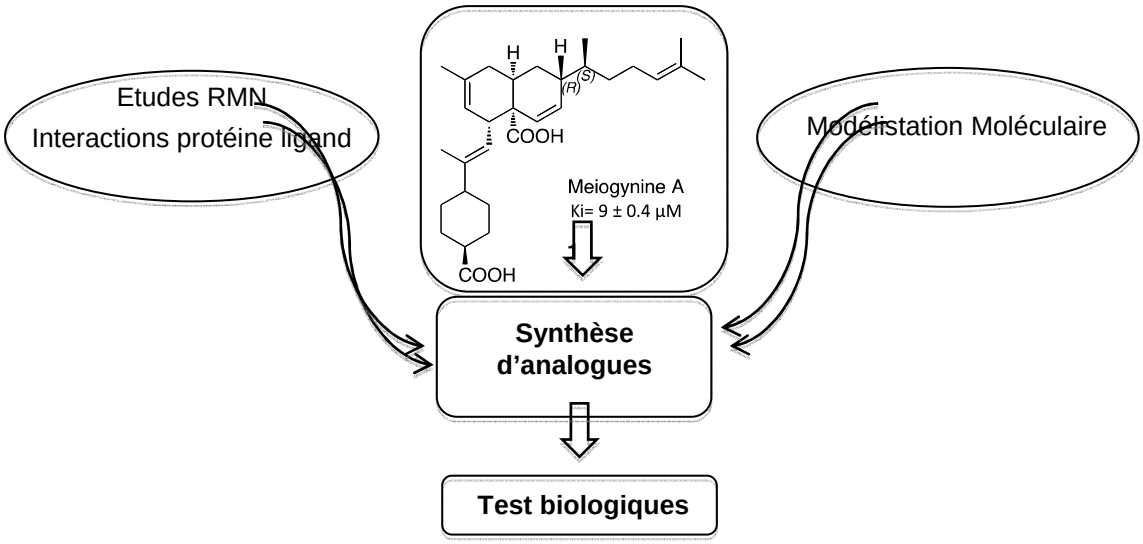
Contexte de l'étude : L'apoptose est le processus par lequel des cellules déclenchent leur auto-destruction en réponse à un signal. C'est un processus indispensable à l'homéostasie de tout organisme pluricellulaire. Dans certains cancers, ce mécanisme est inhibé ce qui entraîne la prolifération des cellules tumorales. L'apoptose est en partie contrôlée, via des interactions protéines-protéines, par la famille des protéines Bcl-2 qui comprend des membres pro-apoptotiques (Bax, bak…) et des membres anti-apoptotiques (Bcl-2, Bcl-xL et Mcl-1…). Afin de trouver des composés originaux permettant de restaurer l'apoptose, notre équipe a criblé des extraits de plantes venant de zones sub-tropicales sur l'interaction Bcl-xL/Bak. C'est ainsi que la meiogynine A (**1**), un triterpène inhibant l'intéraction de Bcl-xL avec Bak, a été isolée d'une plante de Malaisie. Sa **synthèse totale** a été réalisée afin de déterminer sa **configuration absolue**.



Résultats : **La synthèse de** plusieurs analogues **a été réalisée, guidée par des études RMN d'**interactions protéine-ligand **et de modélisation moléculaire. Des résultats biologiques *in vitro* et *in cellulo*** prometteurs **ont d'ores et déjà été obtenus. L'ensemble de cette étude sera présentée.**

Références Bibliographiques :

1) Litaudon, M. ***et al., J. Nat. Prod.*****,** 2009**, *72*, 480-483**
2) Fomekong Fotsop, D**. *et al.*, *J. Org. Chem.*,** 2010**, *75*, 7412–7415**

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NEW SPIROSILANES AS FLUORIDE SENSORS

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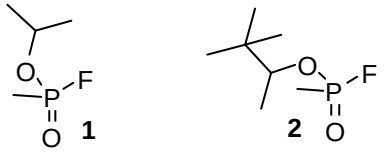
Keywords: pentasilicate, fluoride sensor, organophosphorous, spirosilane

Over last decades, terrorist attacks risks have increased. For this reason, it is very important to have good methods to detect and destroy chemical warfare. We have taken an interest in organophosphorous compounds because some of these such as Sarin (**1)** or Soman (**2)** are extremely toxic (DL_{50} of Sarin < 10 µg/Kg)[1] and stable in water ($t_{1/2}$ of Soman = 82,5 h at pH = 7). Moreover, since 1991, these compounds have been considered as weapons of mass destruction by U.N.O.



Our project consists in use a silane, which can cleave the bond between the phosphorous atom and fluorine atom and trap fluoride ion due to the toxic organophosphorous compounds decomposition. When the silane catches the fluoride, a pentasilicate or a hexasilicate can be created[2]. The hypervalence transition modifies the geometry around the silicon atom. It switches from tetravalent structure to a trigonal bipyramidal structure. We use this modification to detect the organophosphorous compounds presence. We have focused on two kinds of silanes (figure 1)[3] to make our sensors for two reasons. First, their pentasilicalates are stable and can be isolated. Second, with aromatic ring, these silanes exhibit good properties in UV and fluorescence spectroscopies. Currently, we are working on the improvement of the detection limit of ours sensors by functionalization.

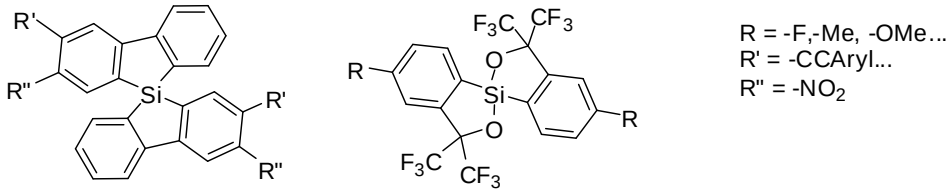


Figure 1 : Spirosilanes used as sensor

Acknowledgments/Financial assistance: DGA

[1] H. P. Benschop, L. P. A. De Jong *Acc. Chem. Res.* **1988**, *21*, 368
[2] C. Chuit, R. J. P. Corriu, C. Reye, J. C. Young, *Chem. Rev.***1993**, *93*, 1371–1448
[3] Martin, J. C. *J. Am. Chem. Soc.* **1985***, 107*, 6340-6352; Klumpp, G. W. *J. Organomet. Chem.* **1997**, *548*, 29-32

TORSION ANGLES MODULATION OF DINUCLEOTIDES USING A PHOSTONE MODIFICATION

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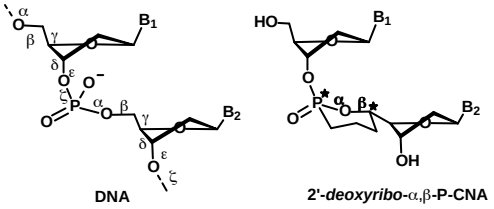
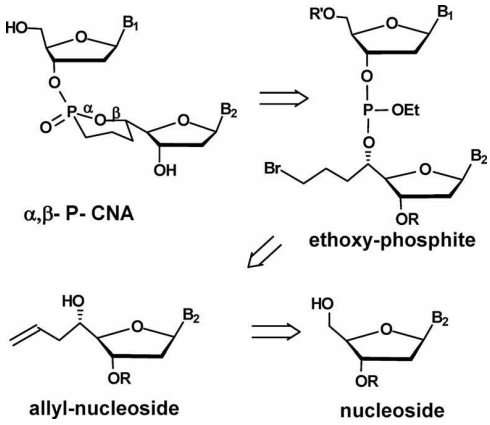
The development of conformationally restricted nucleosides has attracted a lot of attention mainly due to important potential applications of antisense oligonucleotides.[1]

However, much less attention has been devoted to the design of conformationally restricted nucleosides for the special purpose of mimicking biologically important non-helical secondary structures of DNA and RNA[2]. In addition to the double-stranded helical conformation, nucleic acids may adopt many other alternative structures such as bulges, hairpins, U-turns, or branched junctions.[3]



These secondary structures always contain unpaired nucleotides or non-Watson-Crick pairs and are characterized by a variety of backbone conformations that differ markedly from the regular conformational states of double-stranded helices.[4] It is now well-established that these disparate structures play a crucial role in fundamental biological processes where protein-nucleic acid interactions, DNA/RNA folding, or RNA catalytic activity are involved.

Phostone-constrained nucleic acids (P-CNAs) are dinucleotides building blocks in which the torsional angles α and β of the sugar/phosphate backbone are constrained to non-canonical values within a cyclic phosphonate structure (phostone) synthesised by diastereoselective intramolecular Arbuzov reaction improved by microwave activation and LiBr addition. During the synthesis, two additional stereocenters are created allowing altogether the modulation of the torsion angles. Each of the four possible diastereoisomers may have a different canonical or non-canonical conformation.[5]



References

[1] C. J. Leumann, *Bioorg. Med. Chem*. **2002**, *10*, 841 ; A. J. A. Cobb, *Org. Biomol. Chem.* **2007**, *5*, 3260; J. Lebreton, J.-M. Escudier, L. Arzel and C. Len, *Chem. Rev*. **2010**, *110*, 3371 ; C. Z. Zhou and J. Chattopadhyaya, *Curr. Opin. Drug. Disc.*, **2009**, *12*, 876 ; N. M. Bell and J. Micklefield, *ChemBioChem*. **2009**, *10*, 2691.

[2] C. Dupouy, C. Payrastre and J.-M. Escudier, *Target In Heterocyclic Systems: Chemistry and Properties,* Attanasi, O. A.; Spinelli, D., Eds ; Societa Chimica Italiana ; Rome, **2008***, Vol 12* p:185–211.

[3] P. Belmont, J.-F. Constant and M. Demeunynck, *Chem. Soc. Rev*. **2001**, *30*, 70.

[4] B. Schneider, S. Neidle, H. M. Berman, *Biopolymers.* **1997**, *42*, 113 ; C. M. Duarte, A. M. Pyle, *J. Mol. Biol.* **1998**, *284*, 1465.

[5] D.-A. Catana, M. Maturano, C. Payrastre, P. Lavedan, N. Tarrat and J.-M. Escudier, *Eur. J. Org. Chem*. **2011**, *34*, 6857.

EFFORTS TOWARDS THE SYNTHESIS OF THE FRAGMENT C_{30}-C_{52} OF AMPHIDINOL 3

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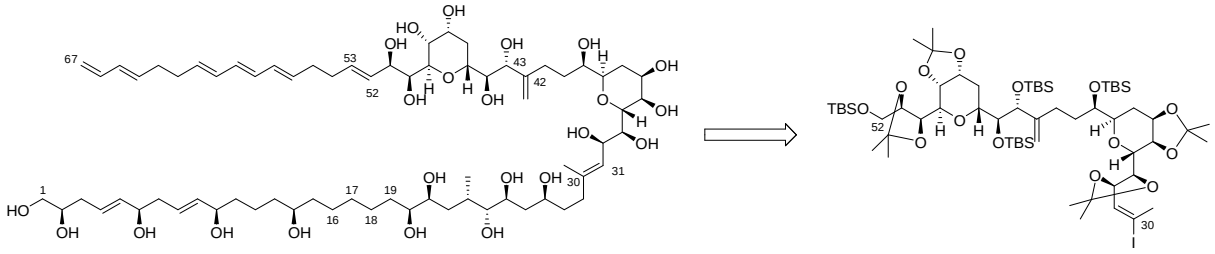
Keywords: total synthesis, cross-couplings, iron catalysis, amphidinol 3.

Amphidinols are a group of metabolites isolated from the marine dinoflagellates *Amphidinium klebsii* and *Amphidinium carterae*.[4] Amphidinol 3 has emerged as an important synthetic target because of its antifungal and hemolytic activities[5] and its challenging structure composed by a skeleton of 67 carbon atoms with 25 stereogenic centers; the absolute stereochemistry has been proposed by Murata and co-workers using *J*-based NMR spectroscopic technique,[6] but it is still being discussed.[7] To date, no total synthesis of Amphidinol 3 has been reported in the literature but a number of groups, including our own,[8] have published the synthesis of advanced fragments.

In this presentation, we will present our synthetic efforts towards the C_{30}-C_{52} fragment of amphidinol 3 which contains two highly substituted tetrahydropyran rings and incorporates 15 of the 25 stereocenters.



Amphidinol 3

[4] Murata, M.; Matsuoka, S.; Matsumori, N.; Paul, G.K.; Tachibana, K. *J. Am. Chem. Soc.* **1999**, *121*, 870.
[5] Houdai, T.; Norsy, N.; Matsumori, N.; Satake, M.; Murata, M. *Tetrahedron* **2005**, *61*, 2795.
[6] Matsumori, N.; Kaneno, D.; Murata, M.; Nakamura, H.; Tachibana, K. *J. Org. Chem.* **1999**, *64*, 866.
[7] (a) Oishi, T.; Kanemoto, M.; Swasono, R.; Matsumori, N.; Murata, M. *Org. Lett.* **2008**, *10*, 5203. (b) Swasono, R.; Kanemoto, M.; Matsumori, N.; Oishi, T.; Murata, M. *Heterocycles* **2011**, *82*, 1359.
[8] (a) Cossy, J.; BouzBouz, S. *Org. Lett.* **2001**, *3*, 1451. (b) Cossy, J.; Ferrié, L.; Tsuchiya, T.; Reymond, S.; Kreuzer, T.; Colobert, F.; Serré, K.; Marko, I. *Synlett* **2007**, *14*, 2286. (c) Colobert, F.; Kreuzer, T.; Cossy, J.; Reymond, S.; Tsuchiya, T.; Ferrié, L.; Marko, I.; Jourdain, P. *Synlett* **2007**, *15*, 2351. (d) Cossy, J.; Tsuchiya, T.; Reymond, S.; Kreuzer, T.; Colobert, F.; Marko, I. *Synlett* **2009**, *16*, 2706.

STUDIES ON THE MECHANISM OF GLYCOSYLATION REACTIONS. DETERMINATION OF PRIMARY ^{13}C KINETIC ISOTOP EFFECTS AT NATUREL ABUNDANCE USING HIGH FIELD NMR METHODS

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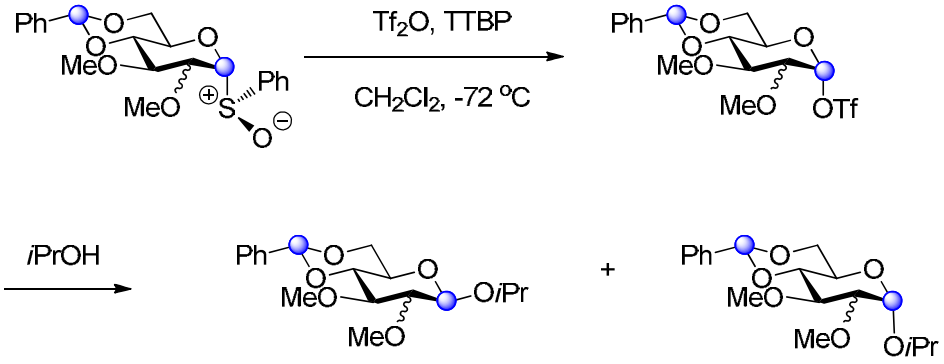
Kinetic isotopic effects (KIEs) are powerful tools to obtain insight into the mechanism of a great range of reactions. We have determined the primary (^{13}C) KIE for model glycosylation reactions by NMR (^{13}C at 200 MHz and ^{1}H at 800 MHz). Glycosylations with 4,6-*O*-benzylidene protected mannosyl- and glucosyl-donors are respectively known to display high β-selectivity and α-selectivity. The experimental KIE for α-mannosylation was in favor of an S_N1-like mechanism whereas that for β-mannosylation suggested a S_N2-like mechanism. Concerning α- and β-glucosylations, we have found similar KIE values suggesting an S_N2-like mechanism for both. We have also calculated the KIEs for these reactions. Experimental and calculated (B3LYP/ 6-31G (d,p) values with a polarizable continuum model) were in good agreement except the α-mannoside .



ORIGINAL DISILANES AS INTERMEDIATES FOR THE SYNTHESIS OF 10-SILATESTOSTERONE

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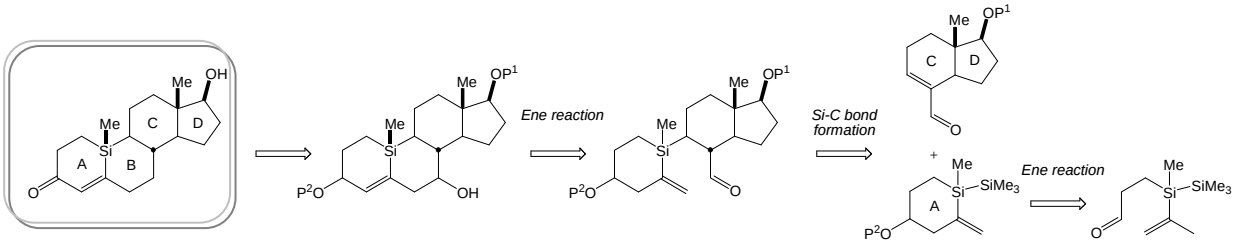
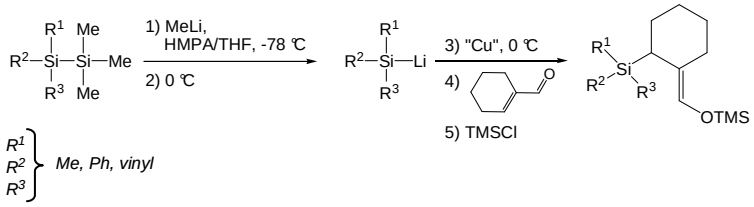
Our current researches are directed toward the synthesis of 10-Silatestosterone. A retrosynthetic pathway has been envisaged as following :



Scheme 1: Retrosynthetic pathway of 10-Silatestosterone (P= Protecting group)

The C&D bicyclic compound is well-known as steroids starting material.[1] Therefore, we turn our attention to the preparation of the A ring. From this perspective we have developed an efficient approach to obtain non-symmetrical and high functionalized disilanes. The cyclization step into the A ring by ene reaction[2] has been optimized.

Additionally the "Si-C bond formation" step is currently studied. The silicon-silicon bond of hexamethyldisilane (simplest disilane in organic chemistry[3]) has been successfully cleaved by MeLi under THF/HMPA conditions. We first trapped the nucleophilic specie with cyclohexenecarboxaldehyde (a C ring model) in a 1,4-addition reaction.



Scheme 2: Si-C bond formation model

Our team is working on extending this method to non-symmetrical disilanes. First results give evidences that we are able to control the selectivity of the Si-Si bond cleavage.

References

1) Lepaje, O.; Stone, C.; Deslongchamps, P. *Org. Lett.* **2002**, *4*, 1091-1094
2) Díez-González, S.; Paugam, R.; Blanco, L. *Eur. J. Org. Chem.* **2008**, 3298-3307
3) A. Giros, *Synlett*. **2012**, DOI: 10.1055/s-0031-1290278

HOW CAN WE INTRODUCE A PERFLUORINATED GROUP IN AN ELECTROPHILIC FASHION?

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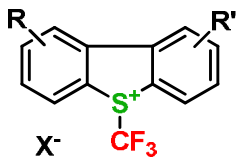
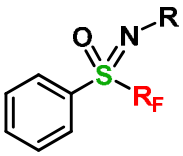
Magical, Fabulous, Fantastic: there are not enough superlatives to describe the positive effects brought by a fluorine atom to a molecule.[1] Introduction of this particular halogen to an organic or inorganic skeleton results indeed, in most cases, in deep enhancement to the induced properties through steric and/or electronic unrivalled effects.[2] As a consequence, all fields of chemistry have taken benefit of the presence of fluorine atoms and everyday life is influenced and facilitated by this halogen. The exhaustive list is too long to describe here but the main applications are located in the domain of energy (electric power, battery), refrigeration, materials (polymers, liquid crystals), agrochemical compounds and last but not least healthcare (medical imagery, drugs).[3]

However, the synthesis of a fluorinated molecule is still far from obvious. This is especially true if the incorporation of the perfluorinated moiety occurs at a late stage of the synthesis of a highly functionalized compound. Even if huge progression has been realized for the invention of selective, stable and friendly reagents, many problems are still unsolved. Furthermore, there is an increasing demand, especially coming from non-specialized laboratories, for easy to prepare and to handle molecules, with emphasis on perfluoroalkylating ones.

After a general and short introduction of the properties of the fluorine atom, this lecture will focused on the very recent and numerous developments in the domain of electrophilic perfluoroalkylating compounds.[4] Our recent contributions in the chemistry of sulfonium salts and sulfoximine derivatives will be detailed.



Sulfonium salts



Sulfoximines

R_F = fluoroalkyl

During this talk, we will also present the versatility offered by the sulfoximine core which allow not only the flexibility of the fluoroalkyl moiety but also can be employed for other purposes as an electronwithdrawing group.

References

1) Chemical and Engineering News, June 5, 2006 Volume 84, Number 23, pp. 15-24.
2) a) T. Hiyama, in: Organofluorine Compounds, Chemistry and Applications, Springer-Verlag, Berlin Heidelberg, **2000**; b) P. Jeschke, *ChemBioChem*, **2004**, *5*, 637-640.
3) P. Kirsch, in *Modern Fluoroorganic Chemistry*, Wiley-VCH, Weinheim, **2004**
4) Y. Macé, E. Magnier, *Eur. J. Org. Chem*. **2012**, DOI:10.1002/ejoc.201101535

Friday Morning

ALTMAYER-HENZIEN Amandine

Synthesis and structural study of aza-modified ACBC oligomers

XU Bixue

Synthesis of monofluoro- and *GEM*-difluoro-carbasugars

HEMELAERE Rémy

Synthesis of 3-(1-alkylidene)phthalides via an original oxidation/isomerisation sequence

DE SCHUTTER Coralie

Conjugated radical addition: addition of phosphonodifluoromethyl radical onto enones

RIFLADE Benoît

Catalysis of new functrionalized hybrids of the Dawson-type POM $[P_2V_3W_{15}O_{62}]^{9-}$

QU Huanhuan

Synthesis and anticancer activities study if glycosphingolipids

LEPRONIER Aymeric

Palladium-catalysed coupling of oxanorbornenes and tertiary propargylic carboxylates: a simple access to allenylidenecyclopropanes

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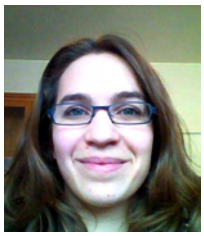
Pr. VIRIEUX David

Phosphorus reagents, a colorful palette
for organic synthesis and new biomolecules



SYNTHESIS AND STRUCTURAL STUDY OF AZA-MODIFIED ACBC OLIGOMERS

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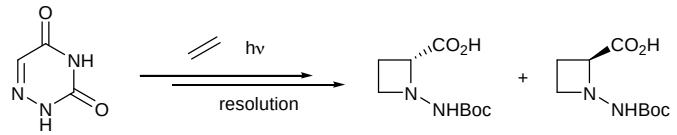
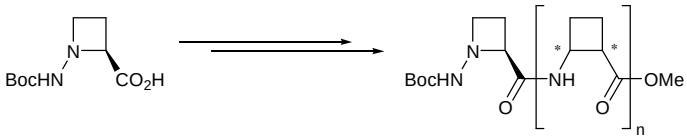
β-Peptides are amongst the most thoroughly investigated peptidomimetic oligomers owing their resistance to proteolytic degradation and to their ability to adopt secondary structure akin to α-peptides. In this respect, cyclic β-amino acids, where both the α and β carbon atoms are part of the ring, are of particular interest since they are conformationally restricted. Oligomers of 5- and 6-membered ring β-amino acids have been shown to adopt regular structures such as sheets or helices. Our interest focuses on 4-membered ring β-amino acids. Indeed, it has been recently reported that oligomers of *cis*-cyclobutane β-amino acid (ACBC) adopt a strand-type structure[1] whereas oligomers of *trans*-ACBC form a 12-helix.[2]

These results prompted us to study 1-aminoazetidinecarboxylic acid (AAzC), an *aza*-analogue of ACBC, which can potentially adopt either a *cis* or *trans* structure due to the configurational flexibility of the pyramidal nitrogen atom that replaces the β-carbon of ACBC. We have developed a short and efficient synthesis of this original cyclic hydrazino acid in enantiomerically pure form using a new extension of our [2 + 2] photocycloaddition methodology.[3]



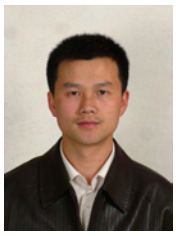
We are currently investigating the consequences of the replacement of the *N*-terminal ACBC residu of both all *trans* and all *cis* ACBC-oligomers by an AAzC residu.



In this communication, we will describe the synthesis of hetero-oligomers containing AAzC and *cis* or *trans*-ACBC and we will present our observations on the structural preferences of this original amino acid as a constituent of a peptide.[4]

References

1) Rùa, F.; Boussert, S.; Parella, T.; Díez-Pérez, I.; Branchadell, V.; Giralt, E.; Ortuño, R. M. *Org. Lett.*, **2007**, *9*, 3643-3645
2) Fernandes, C.; Faure, S.; Pereira, E.; Théry, V.; Declerck, V.; Guillot, R.; Aitken, D. J. *Org. Lett.* **2010**, *12*, 3606-3609
3) Declerck, V.; Aitken, D. J. *J. Org. Chem.* **2011**, *76*, 708-711
4) Altmayer-Henzien, A.; Declerck, V.; Guillot, R.; Aitken, D. J. *Manuscript in preparation*



SYNTHESIS OF MONOFLUORO- AND *GEM*-DIFLUORO-CARBASUGARS

Bixue XU, Dr. Yongmin ZHANG, Dr. Melanie ETHEVE-QUELQUEJEU, Prof.Matthieu SOLLOGOUB*

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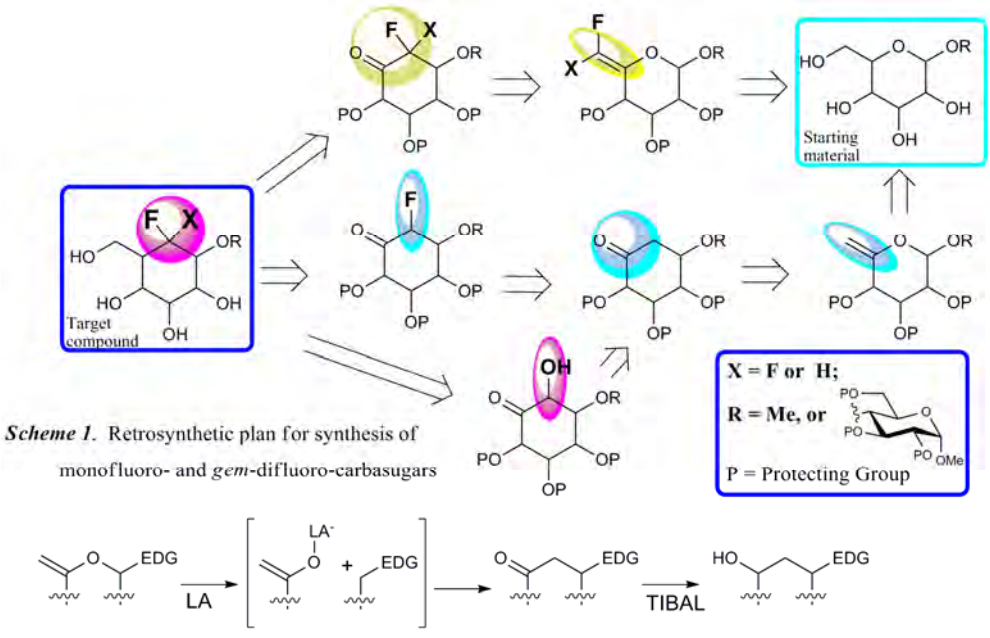
Keywords: Carbasugars; Fluorine; Mimics.

Carbasugars are strictly defined as sugar analogues in which the endocyclic oxygen atom has been replaced by a methylene group. Such replacement has the inherent disadvantage to suppress any possible hydrogen bond formation that involved this electronegative atom.[1] One way to circumvent this problem is to replace the endocyclic CH_2 group by a CFH or CF_2 moiety in a carbasugar. We have first synthesized *gem*-difluoro-carbaglucose,[2] *gem*-difluoro-carbamannopyranose and *gem*-difluoro-carbagalactopyranose.[3] In this work, we present the synthesis of Monofluoro- and *gem*-Difluoro-Carbasugars analogues of mono- and disaccharides with the retrosynthetic plan illustrated in Scheme 1. Our strategy is based on a Lewis acid, triisobutylaluminum (TIBAL)[4] or $Cl_3TiOiPr$,[5] induced rearrangement of an enolether possessing an electron-donating group as illustrated in Scheme 2.[6]



Scheme 1. Retrosynthetic plan for synthesis of monofluoro- and *gem*-difluoro-carbasugars

Scheme 2. General rearrangement of EDG-substituted vinyl ethers. EDG= electron-donating group, LA=Lewis acid, TIBAL=triisobutylaluminum.

Acknowledgments: We thank the China Scholarship Council for a PhD fellowship to Bixue XU.

References

1. Montero, E.; Garcia-Herrero, A.; Asensio, J. L.; Hirai, K.; Ogawa, S.; Santoyo-Gonzalez, F.; Canada, F. J.; Jimenez-Barbero, J. *Eur. J. Org. Chem*. **2000**, 1945-1952;
2. Deleuze, A.; Menozzi, C.; Sollogoub, M.; Sinaÿ, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 6680-6683;
3. Sardinha, J; Guieu, S; Deleuze, A; Fernández-Alonso, M. C.; Rauter, A. P.; Sinaÿ, P.; Marrot, J.; Jiménez-Barbero, J.; Sollogoub, M. *Carbohydr. Res*., **2007**, *342*, 1689 - 1703;
4. Das, S. K.; Mallet, J.-M.; Sinaÿ, P. *Angew. Chem. Int. Ed. Engl*. **1997**, *36*, 493 – 496;
5. Sollogoub, M.; Mallet, J.-M.; Sinaÿ, P. *Tetrahedron Lett*. **1998**, *39*, 3471- 3472;
6. Sollogoub, M.; Mallet, J.-M.; Sinaÿ, P. *Angew. Chem. Int. Ed*. **2000**, *39*, 362-364.

SYNTHESIS OF 3-(1-ALKYLIDENE)PHTHALIDES VIA AN ORIGINAL OXYDATION / ISOMERIZATION SEQUENCE

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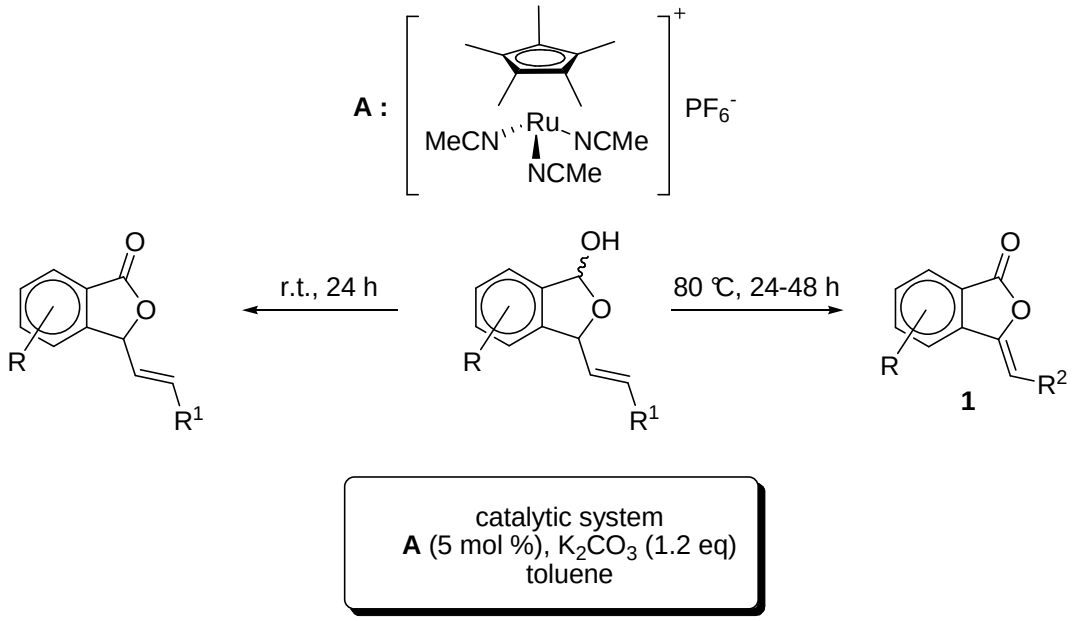
A tandem reaction is a reaction in which several bonds are formed in sequence without isolating intermediates, changing reaction conditions, or adding reagents. This strategy combines structural diversity with eco-compatibility. Development of tandem reactions involving an isomerization process with the same catalyst also is clearly an area of research for the future. Recently, we described that pentamethylcyclopentadienyl ruthenium is an efficient catalyst for the redox isomerisation of functionalized allylic alcohols into carbonyl compounds.[1] We reported here a new access of 3-alkylidenephtalides via an oxidation/isomerization tandem reaction using $[RuCp^*(MeCN)_3][PF_6]$ catalyst. When the reaction is conducted at room temperature with the same catalytic system, oxidative process is only observed. (*Z*)-3-(1-alkylidene)phthalides **1** represent an important class of naturally occurring lactones, which are characterized by interesting biological properties. As application of this strategy, we prepared natural (*Z*)-3-*n*butylidenephtalide, which have in vitro and in vivo anti-cancer effect. [2]



References
1 Helou, M.; Renaud, J. L.; Demerseman, B.; Carreaux, F.; Bruneau, C. *New. J. Chem*., **2008**, *32*, 929. Bouziane, A.; Carboni, B.; Bruneau, C. ; Carreaux, F.; Renaud, J. L., *Tetrahedron*, **2008**, *64*, 11745. Bouziane, A.; Régnier, T.; Carreaux, F.; Carboni, B. ; Bruneau, C.; Renaud, J. L., *Synlett*, **2010**, 207.
2 N.M. Tsai, Y.L. Chen, C.C. Lee, P. C. Lin, P.C. Lin, Y.L. Cheng, W.L. Chang, S.Z. Lin, H.J. Harn, *J. Neurochem*, **2006**, 99, 1251.

CONJUGATED RADICAL ADDITION: ADDITION OF PHOSPHONODIFLUOROMETHYL RADICAL ONTO ENONES

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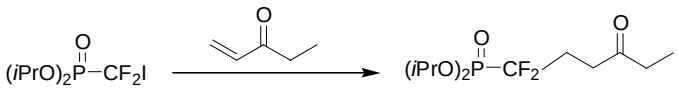
Due to the limitation of phosphonates as biological models of phosphates, difluoromethylphosphonates have been introduced as stable and isopolar phosphate mimics.[1] This new class of phosphate analogs provided a powerful arsenal of biological probes for examination or perturbation of the mechanisms of phosphoryl transfer enzymes. Their efficiency has been established through many examples of high affinity enzyme inhibitors, and difluoromethylphosphonates emerge as excellent pyrophosphate and phosphate surrogates.[2]

Although the addition of alkyl carbethoxydifluoromethyl free radical onto alkenes has been largely applied,[3] the introduction of the dialkyl phosphonodifluoromethyl group by free radical addition has been partially studied. The formation of this radical from thioether with tri-*n*-butyltin hydride and AIBN has already been described.[4] Because of the high toxicity of tin, another pathway starting from iodo- and bromo-difluoromethylphosphonate using palladium or cobalt complex and even sodium dithionite were also reported.[5] Recently we discovered that the conjugated addition reaction of this radical was possible in the presence of triethyl borane. Our latest results will be presented.



This approach offers a real alternative to the anionic Michael addition.

1. Blackburn, G. M.; Kent, D. E.; Kolkmann, F. *J. Chem. Soc. Chem. Commun.* **1981**, 1188-1190. Blackburn, G. M.; Kent, D. E.; Kolkmann, F. *J. Chem. Soc. Perkin Trans. 1* **1984**, 1119-1125. McKenna, C. E.; Shen, P.–D. *J. Org. Chem.* **1981**, *46*, 4573-4576.
2. Romanenko, V. D.; Kukhar, V. P. *Chem. Rev.* **2006**, *106*, 3868-3935.
3. Yang, Z.-Y.; Burton, D. J. *J. Org. Chem.* **1991**, *56*, 5125-5132. Godineau, E.; Schenk, K.; Landais, Y. *J. Org. Chem.* **2008**, *73*, 6983-6993.
4. Lequeux, T.; Lebouc, F.; Lopin, C.; Yang, H.; Gouhier, G.; Piettre, S. R. *Org. Lett.* **2001**, *3*, 185-188. Pignard, S.; Lopin, C.; Gouhier, G.; Piettre, S. R. *J. Org. Chem.* **2006**, *71*, 31-37.
5. Yang, Z.-Y.; Burton, D. J. *Tetrahedron Lett.* **1991**, *32*, 1019-1022. Hu, C.-M.; Chen, J. *J. Chem. Soc. Perkin Trans. 1* **1993**, 327-330. Yang, X.; Zhu, Y.; Fang, X.; Yang, X.; Wu, F.; Shen, Y. *J. Fluorine Chem.* **2007**, *128*, 174-178.

CATALYSIS OF NEW FUNCTIONALIZED HYBRIDS OF THE DAWSON-TYPE POM $[P_2V_3W_{15}O_{62}]^{9-}$

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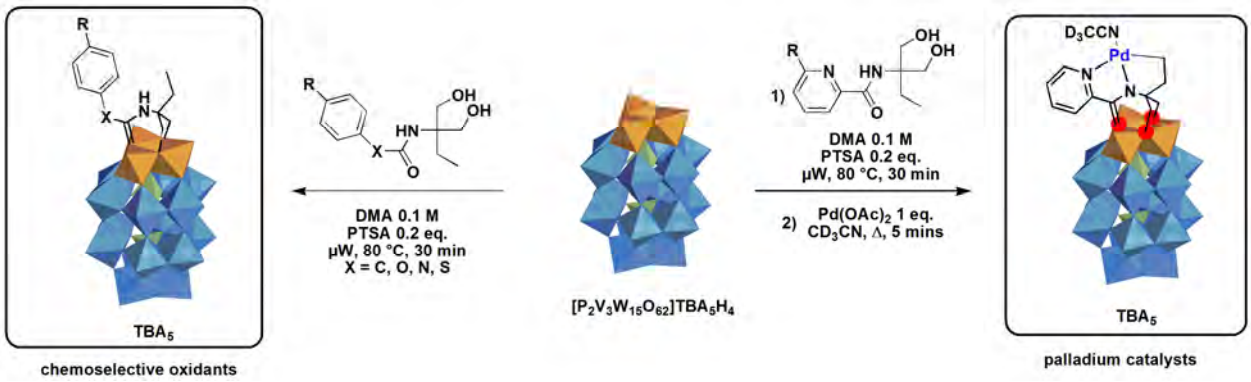
Polyoxometalates (POMs) are a large family of metal-oxygen clusters of early transition metals in high oxidation states with great catalytic applications. Functionalization of the basic structures of polyoxometalates by grafting organic molecules is a way to increase the diversity of these inorganic clusters, as well as to possibly tune the catalytic activity.[1]

We will present the grafting of diol-amides to the Dawson tungstovanadate $TBA_5H_4[P_2V_3W_{15}O_{62}]$,[2] which gives a new family of functionalized POMs featuring the unprecedented substitution of a POM oxo bridging ligand with the carbonyl oxygen of the amide group. These hybrids were used as catalysts for chemoselective oxidation.[3]

Moreover, using a specific pyridine ligand, we achieved the synthesis of a new type of late transition metal containing POM where an indirect connection between the metal and the POM takes place through the ligand. These new POMs were successfully used as palladium catalysts.



<u>References</u>

[1] D.-L. Long, R. Tsunashima, L. Cronin, *Angew. Chem., Int. Ed.* **2010**, *49*, 2.
[2] J. Li, I. Huth, L.-M. Chamoreau, B. Hasenknopf, E. Lacôte, S. Thorimbert, M. Malacria, *Angew. Chem., Int. Ed.* **2009**, *48*, 2035.
[3] J. Oble, B. Riflade, A. Noël, M. Malacria, S. Thorimbert, B. Hasenknopf, E. Lacôte, *Org. Lett.* **2011**, *13*, 5990.

SYNTHESIS AND ANTICANCER ACTIVITIES STUDY OF GLYCOSPHINGOLIPIDS

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Keywords: glycosphingolipids; synthesis; anticancer.

Glycosphingolipids (GSLs) are cell-surface antigens, it was suggested that changes in their composition would result in changes in the ability to bind antibody and ability to induce immune response of the tumor cells expressing them[1]. The idea of GSLs as tumor-associated antigens is the basis for attempts to utilize them for anticancer vaccine development[2]. Recently, our research group focused on GM3 (Fig. 1) which was expressed in melanoma and many other human and animal cancers[3].

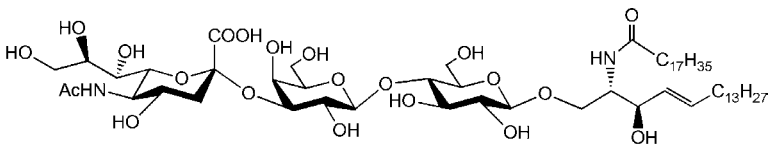

Fig. 1 GM3 glycosphingolipid antigen

Based on the structure modification of GM3, we have successfully synthesized several analogues (Fig. 2) of this type of glycosphingolipid antigen.

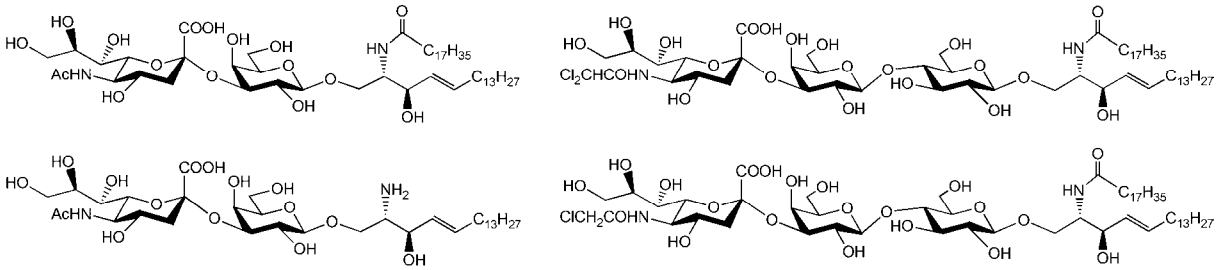

Fig. 2 Target glycosphingolipid antigens

Going a step further, these target glycosphingolipids obtained will be used for screening anticancer agents.

Acknowledgments/Financial assistance: China Scholarship Council (CSC)

References

1. Hakomori, S. J. Biol. Chem. 1990, 265,18713-18716.
2. Tillack, T. W.; Allietta, M.; Moran, R. E.; Young, W. W. J. Biochim. Biophys. Acta. 1983, 733, 15-24.
3. Zhang, Y. Iwabuchi, K. Nunomura, S. Hakomori, S. Biochemistry. 2000, 39, 2459-2468.