MP124

PREPARATION OF PORPHYRINS AND THEIR CROSS-COUPLING REACTIONS WITH OLIGOTHIOPHENES

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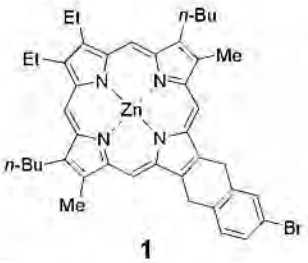
Increasing interest has been focussed on porphyrin derivatives as an opt-electronic material, organic thin film transistor, organic light-emitting diode, and so on. Preparation of such porphyrins is one of the hottest topics in organic synthesis. For the construction of such porphyrins, porphyrins with simple functional groups are first prepared by the established the functional groups. Cross-coupling reaction is such a common method for introduction of functional groups for the synthesis of the porphyrin derivatives. We are interested in the preparation of a single-electron organic device which consists of a porphyrin derivative as a molecular dot and an oligothiophene derivative as a molecular wire. For the preparation of these chromophores are spatially separated by some rigid spacers. We planned to prepare a new type of porphyrins with bromoacene units 1, 2, and 3 as shown below for cross-coupling reactions.



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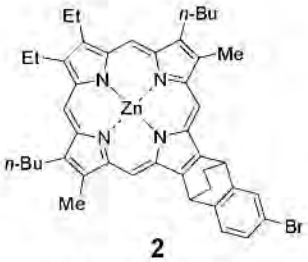

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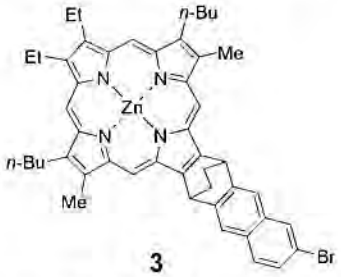

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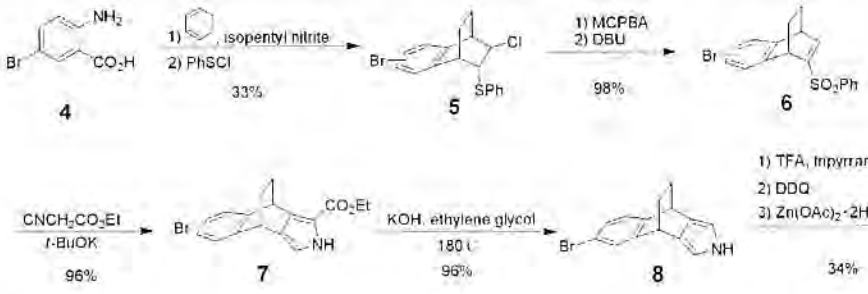
The new porphyrin 2 was prepared by the [3+1] condensation of a pyrrole derivative with the known tripyrrane[1] as follows. Benzyne generated from 5-bromoanthranilic acid (4) reacted with 1,3-cyclohexadiene to give bromoethanonaphthalene, which was then treated with benzenesulfenyl chloride to give 5. Sulfide 5 was oxidized with MCPBA and then elimination of HCl with DBU afforded 6. Barton-Zard pyrrole synthesis of 6 with isocyanoacetate gave pyrrole 7. Removal of the ester moiety from 7 was achieved by heating 7 with KOH in ethylene glycol at 180 °C for 2 h. The obtained α-free pyrrole 8 was reacted with the tripyrrane to afford the targeted porphyrin 2. Other porphyrins were similarly prepared. Now, we examine the coupling reactions of porphyrins 1-3 with oligothiophene derivatives under various conditions. The results will be discussed in the session.



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MP125

CATALYTIC ENANTIOSELECTIVE CONJUGATE FRIEDEL-CRAFTS ALKYLATIONS EMPLOYING SULFONYL-FUNCTIONALIZED ENONES AS TEMPLATES

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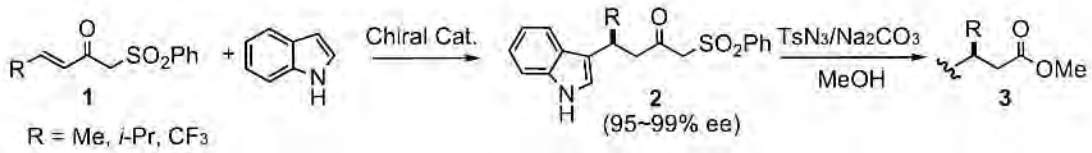
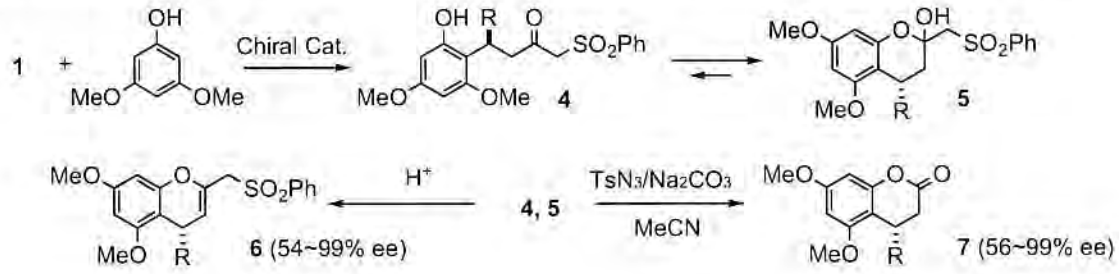
The conjugate Friedel-Crafts alkylation reaction of aromatic compounds to alkenes leading to formation of a new C-C bond is a important in synthetic chemistry. However, the catalytic asymmetric version of conjugate Friedel-Crafts reaction has been remained for long-term as an unexplored field. Such a reaction would provide a simple and attractive method for the formation of optically active aryl-substituted compounds from easily available starting materials. To the best of our knowledge, chiral Lewis acid-catalyzed Friedel-Crafts alkylation of electron-rich aromatic compounds to electron-deficient alkenes has been pioneered by Jørgensen. [1]
On the other hand, we developed catalytic asymmetric hetero Diels-Alder reactions with vinyl ethers and ordinary Diels-Alder reactions with cyclopentadiene by the use of sulfonyl-functionalized α,β-unsaturated ketones 1 as new type of hetero 1,3-dienes and dienophiles, respectively.[2] Our continuing interest has been focussed on utilization of these sulfonyl-functionalized enones 1 as achiral templates for Lewis acid-catalyzed enantioselective carbon-carbon bond formation. Thus, our attention was directed the development of chiral Lewis acid-catalyzed asymmetric conjugate addition of aromatic compounds to enones 1. The reaction of Indole to enones 1 was first successfully achieved to provide the conjugate addition products 2 in good yields and high enantioselectivities (95~99% ee) by the use of chiral Lewis acid catalysts. The β-keto sulfone moiety in 2 was readily transformed into ester group.



During our investigation on asymmetric conjugate Friedel-Crafts alkylations, we have quite recently found that the conjugate addition reactions of 3,5-dimethoxyphenol to enones 1 were also effectively catalyzed by chiral Lewis acid to produce the corresponding conjugate addition products, which exsisted almost in the hemiacetal forms 5. A mixture of 4 and 5 has been transformed into both dihydrobenzopyrans 6 and hydrocoumarins 7 in moderate to high enantioselectivities (54~99% ee).



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MP126

SYNTHESIS AND SURFACE PROPERTIES OF FLUOROUS SURFACTANTS BASED ON 1,2,3-TRIAZOLES

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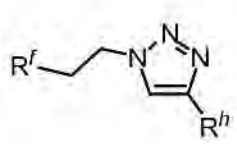
Fluorous surfactants have found use in primarily delivery systems for drugs and other bioactive agents, and as molecular tools in biomedical applications. Moreover, fluorinated surfactants are much more surface active and more efficient than their hydrocarbon counterparts.[1] We have begun a program of investigation towards fluorous surfactants that are based on a heterocyclic core. We are particularly interested in investigating their self-assembly properties and applications in biology.

We describe here methods for the preparation of polyfluoroalkyl-1,2,3-triazoles 1 – 3 using "Click" chemistry.[2] The impact of variations in perfluoroalkyl (R^f) and hydrocarbon (R^h) chain length, position of substitution, and spacer group length and type on surface tension have also been assessed as a measure of surface activity.



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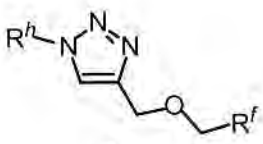

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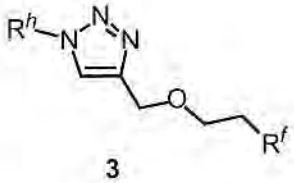

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Surface tension was generally observed to decrease non-linearly with increasing concentrations of the triazoles in *m*-xylene. In series 2 and 3, surface tension decreased with increasing chain length of both fluorocarbon and hydrocarbon, and with fluorine content. For series 1, when the hydrocarbon chain was C_4-C_6 in length, similar decreases in surface tension were observed with increasing fluorocarbon chain length, but when the hydrocarbon chain contained 8 carbons, the surface tension behaviour was more complex, which suggested that the hydrocarbon played a dominant role.

Similar analyses across a range of variations in structures 1 - 3 have revealed equally interesting structure-activity relationships that will be outlined in the paper. These imply that molecules with an ether link in the sidechain, as in 2 and 3, will probably serve as more reliable surfactants than compounds of type 1.

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MP127

PEPTIDE VASODILATORS AS ANTI-CANCER DRUG DELIVERY VEHICLES

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Tumour regression is of paramount importance in the war against cancer. It is vital that cancer be controlled and ultimately curtailed. Vasodilating agents are known to also dilate blood vessels in tumours[1]. Vasodilating agents such as bradykinin [2,3] will be employed in an effort to transport anticancer therapeutics into tumours. Preliminary results will be presented that report on a new project that aims to investigate the use of vasodilators to invade and smuggle anti-cancer agents into tumours. This proposal will combine vasodilator chemistry with cyclodextrin, new aromatic heterocyclic and sulphonamide chemistries and in some cases metals (ex. Pt, Cs, Ga) in the quest for new cancer therapies[4-6]. There appears to be little reported on actual peptide-heterocyclic or peptide-sulphonamide drugs in the fight against any diseases let alone cancer although short peptides/amino acids have been used to a degree[7-9]. The total preparation of these species from solid phase protocols appears non-existent. Plans for safer delivery of these anticancer agents will also be discussed. In addition to path-finding "invade and kill" therapies of tumour systems, the results of this project should lead to a better of understanding of targeting and delivery to not only cancer sites but also sites of other afflictions as well.

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2. Iyer AK, Khaled G, Fang J and Maeda. Exploiting the Enhanced Permeability and Retention Effect for Tumor Targeting. *Drug Discovery Today*, 2006; 11, (17/18), 812-818.
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MP128

SYNTHESIS OF INDOLE ANALOGUES OF THE ANTI-*HELICOBACTER PYLORI* COMPOUNDS CJ-13,015, CJ-13,102, CJ-13,104 AND CJ-13,108

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Helicobacter pylori are microaerophilic, gram negative bacteria[1] which colonise the stomach of over half the world's population[2] and have an etiological role in several diseases, including gastric and duodenal ulcers, distal gastric cancer and MALT lymphoma.[3] Current treatment regimes for the eradication of H. pylori are complex and have considerable negative side effects. These factors, as well as increasing bacterial resistance to current antibiotics, render the development of novel specific anti-H. pylori agents an important goal.[4]

CJ-13,015, CJ-13,102, CJ-13,104 and CJ-13,108, are four members of a family 5,7-dimethoxyphthalide containing natural products isolated in 1997 which exhibit selective anti-H. pylori activity.[5] 4,6-Dimethoxyindole analogues of these four naturally occurring antibiotics have been synthesised. It is envisaged that these 4,6-dimethoxyindole analogues, 1-4 respectively, will exhibit more potent and selective activity against H. pylori than the 5,7-dimethoxyphthalide natural products.

The synthetic strategy adopted involved the synthesis of all four analogues from a common advanced intermediate 5 which was synthesized in five steps via N-alkylation of 4,6-dimethoxyindole 6 with bromoalkene 7 with further extension of the alkyl chain by the addition of 3-butenyl magnesium bromide 8 to the derived aldehyde 9. Oxidation (in the case of 1), acetylation (for 2), or Barton-McCombie deoxygenation (for 4) of intermediate 5 was followed by Wacker oxidation to install the 13' ketone functionality common to all three analogues. Reduction of 4 afforded the final analogue, 3.

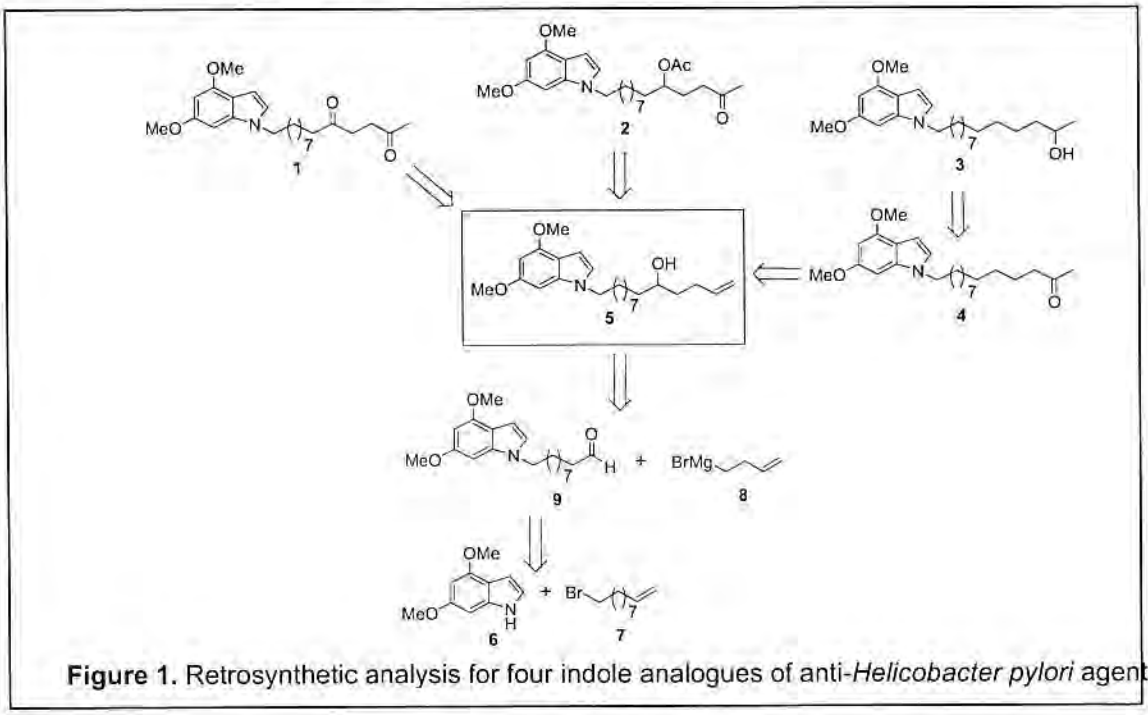

Figure 1. Retrosynthetic analysis for four indole analogues of anti-*Helicobacter pylori* agents

References:

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MP129

STUDIES TOWARDS THE SYNTHESIS OF CELOGENTIN C

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The celogentins contain an unusual structural feature in which the central tryptophan residue contains a link between the C2-carbon with the imidazole-ring of L-histidine, and a C6-linkage with the β-carbon of the leucine residue. Celogentin C, in particular, exhibits high anti-tubulin activity and is a potential target as an antimitotic drug.

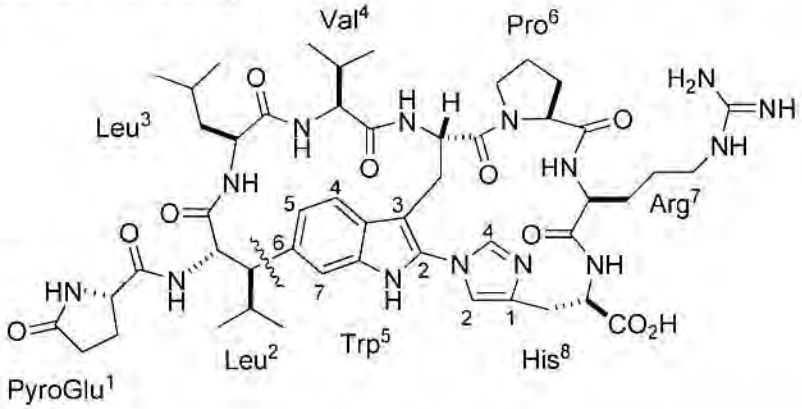
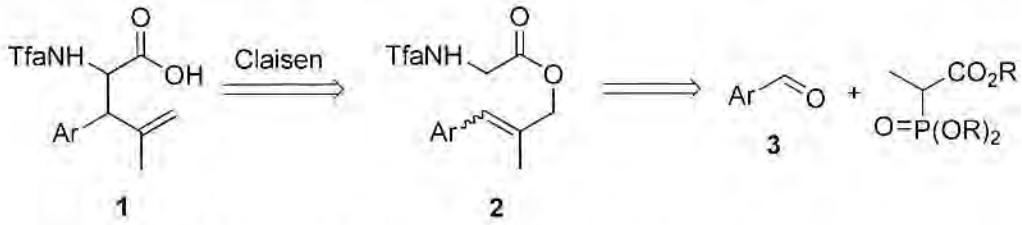


Figure 1. Key bond disconnection of celogentin C under investigation.

Our approach to the leucine–tryptophan linkage involves a Claisen ester-enolate rearrangement which will allow stereoselective synthesis towards other β-aryl leucine derivates (Scheme 1).



Scheme 1. Retrosynthesis of the leucinyl fragment.

MP130

THE DESIGN AND SYNTHESIS OF BIDENTATE PHENANTHRIDINES AS INHIBITORS OF BCL-X_L

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Apoptosis is a common physiological process by which damaged or unwanted cells are eliminated in multicellular organisms. Many cancer cells, however, develop resistance to apoptosis by overproducing anti-apoptotic proteins such as Bcl2 and Bcl-X_L.[1] One strategy for the development of therapeutics for cancer chemotherapy is to target these anti-apoptotic proteins. Small molecule inhibitors of Bcl-X_L such as the BH3I molecules and ABT-737 have been reported.[2,3] Recently, Yu *et al*. identified chelerythrine as an inhibitor of Bcl-X_L through high-throughput screening of natural products.[4] Investigations using NMR spectroscopy show that despite their structural similarity, chelerythrine and its homologue sanguinarine bind at different sites on the Bcl-X_L protein.[5] Based on the docking results obtained using Autodock™, we have designed and synthesized a number of monomer and bidentate phenanthridinium salts that are structurally related to chelerythrine and sanguinarine. The synthesis of the bidentate phenanthridinium salts involves a convergent approach to form two phenanthridinone fragments via the corresponding benzamides. The reduction of *N*-MOM protected phenanthridinones by DIBAL-H results in the formation of the corresponding *N*-methyl phenanthridinium species. The biological activities of these phenanthridinium salts were assessed using fluorescence polarization assay (FPA) and cell viability WST assay. Some of the synthetic phenanthridiniums show higher or equal activities in the FPA assay which is consistent with the predicted docking result from Autodock. However, the synthetic analogues tested so far display weaker cytotoxicity than the natural products.

References:

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MP131

LEWIS ACID-MEDIATED ENANTIOSELECTIVE 1,3-DIPOLAR CYCLOADDITIONS OF BENZONITRILE OXIDE

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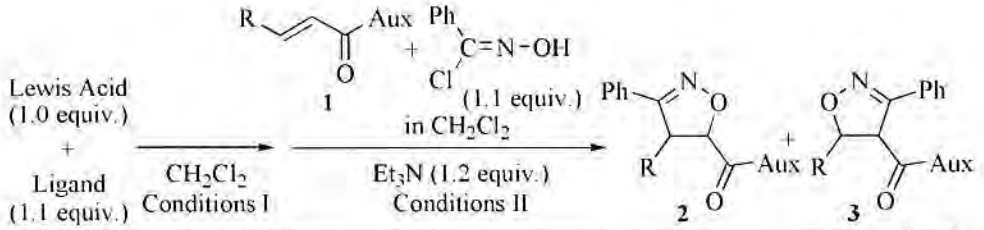
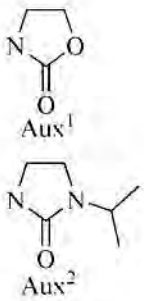
Nitrile oxides are chemical species that are very useful for organic synthesis to yield 5-membered heterocyclic compounds in 1,3-dipolar cycloaddition reactions with dipolarophiles such as alkenes, alkynes, aldehydes, ketones and nitriles.

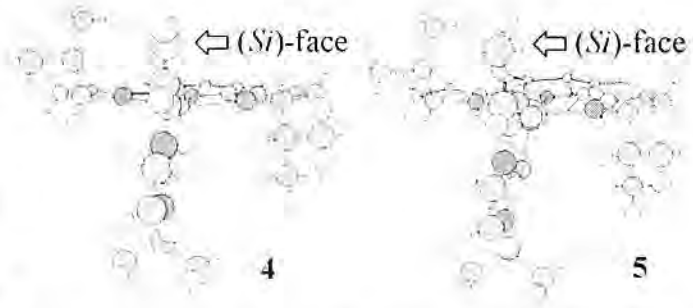
Herein, described are asymmetric 1,3-dipolar cycloaddition reactions of nitrile oxides mediated by pybox–ytterbium triflates, –magnesium bromide, and –magnesium perchlorate. In reactions with a dipolarophile bearing oxazolidinone as a coordination auxiliary, an enantiomer excess (69%*ee*) of the corresponding cycloaddition product was achieved by cycloadditon reaction at 35 °C in the presence of $Yb(OTf)_3$/ph-pybox. Relatively low temperature (–78 °C) was required to obtain enantiomer excesses such as 69%*ee* and 87%*ee* of reactions with a dipolarophile bearing an imidazolidinone group where the reaction is peformed in the presence of $MgBr_2$/ip-pybox to afford cycloadducts.



R	Aux	Lewis Aicd	Ligand	Condition I	Condition II	2 / %	3 / %
H	Aux^1	$Yb(OTf)_3$	(*R*)-ph-pybox	r.t., 3 h	35 °C, 1 h	35 (69, *R*)	-
H	Aux^1	$Yb(OTf)_3$	(*R*)-ph-pybox	r.t., 3 h	r.t., 3 h	61 (43, *R*)	-
H	Aux^2	$MgBr_2$	(S)-ip-pybox	0 °C, 6 h	0 °C, 6 h	80 (38, *S*)	-
H	Aux^2	$MgBr_2$	(S)-ip-pybox	-78 °C, 6 h	-78 °C, 24 h	50 (69, *S*)	-
H	Aux^2	$MgBr_2$	(S)-ip-pybox	-40 °C, 6 h	-78 °C, 24 h	53 (87, *S*)	-
Me	Aux^2	$MgBr_2$	(S)-ip-pybox	r.t., 3 h	0 °C, 24 h	91 (42)	0
Me	Aux^2	$Mg(ClO_4)_2$	(S)-ip-pybox	r.t., 3 h	0 °C, 24 h	85 (69)	3



The Density Functional Theory calculations at the B3LYP/6-31G* level theory were used to optimize geometry of two Mg^{2+}/(*S*)-ip-pybox complexes 4 and 5, Mg^{2+}/(S)-ip-pybox/1 (Aux^2, R=H) and Mg^{2+}/(S)-ip-pybox/1 (Aux^2, R=Me), using the Gaussian 03 program. Mg^{2+} ions in both complexes take distorted trigonal bipyramidal molecular geometry. Directions of isopropyl groups are closely related to the face selection of nitrile oxides which react with C=C bond in dipolarophiles. The (*Si*)-face of dipolarophile is less crowded than the (*Re*)-face because of the direction of the isopropyl group on ip-pybox. The reaction from the former face produces the (*S*)-isoxazoline as aforementioned.



MP132

SYNTHESIS OF NOVEL PORPHYRINOGEN-LIKE MACROCYCLE SCHIFF BASE

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P.R China

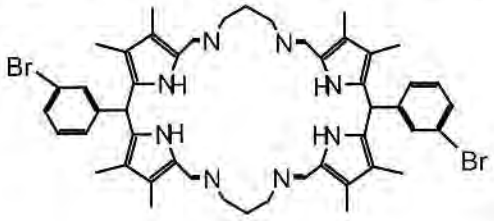
In this paper, a novel porphyrinogen-like macrocycle compound was synthesized and characterized with elemental analyses, ^{1}H NMR, FAB-Ms, and IR methods. The way prepared the compound is as follows:

(1). 3-Bromoformylbenzene (12mmol) and 2-(ethoxycarbonyl)-3,4-dimethylpyrrole[1] (24mmol) were dissolved with heating in 40mL of absolute EtOH. The reaction mixture was then heated to reflux, and 1.2 mL of 6mol/L HCl was added. the product (*A*) was crystallized. It was filtrated, washed with cold EtOH, and dried to yield 4.57g (76%) of *A*.

(2). 10mmol of *A* was suspended in 60mL of absolute EtOH and brought to reflux. A total of 5mL of 5M NaOH solution was added, and the reaction mixture was refluxed for 20h under N_2. The EtOH was removed under reduced pressure, and the residue was diluted with 100mL of H_2O and filtrated. The filtrate was acidified with glacial HOAc, and the diacid was precipitated as a pink solid. The pink solid was dissolved in 60mL of degassed ethanolamine. The mixture was placed under N_2 and refluxed for 2h, after which the reaction mixture was poured into 80mL of ice H_2O while still warm. A solid (*B*) soon separated, which was filtrated and dried to yield 3.11g (87%) of *B*.

(3). 10mmol of *B* was added to 30mL of DMF. The mixture was cooled to –5□, then 12mL of $POCl_3$ was added, after which, the reaction mixture was stilled for 12h under room temperature. The reaction mixture was placed under 50□~60□ and refluxed for 2h, after which the reaction mixture was poured into 100mL of ice H_2O while still warm.. The filtrate was basified with 5M NaOH to pH=9, a brown solid (*C*) separated, which was filtrated and dried to yield 2.02g (49%) of *C*.

(4). 1mmol of *C* was dissolved with heating in 50mL CH_3OH. The reaction mixture was then heated to reflux, 50mL $NH_2CH_2CH_2NH_2$ of CH_3OH solution (2.0×10^{-2}mol/L) was then added tardily. The reaction mixture was refluxed for 4h. The CH_3OH was removed under reduced pressure. The residue (H_4L) was filtrated and recrystallized with CH_3OH, dried to yield 0.37g (82%) of H_4L. H_4L $C_{48}H_{54}N_8Br_2$, [Found: C, 63.87 (63.86), H, 5.85 (6.03), N, 12.24 (12.41)] ^{1}H NMR:δ8.01 (4H,s, HC=N) δ7.11 (12H, m, 8×ArH, 4×NH), δ5.50 (2H, s, CH), δ3.50 (8H, t, CH_2), δ2.09 (12H, s, CH_3), δ2.01 (12H, s, CH_3), δ1.22 (4H, tt, CH_2). FAB-MS m/z: 905 $[H_4L+H]^+$. The melting point of H_4L is 267~268□.



H_4L

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MP133

SYNTHESIS OF IMINOSUGARS VIA POLYHYDROXYLATED NITRONES

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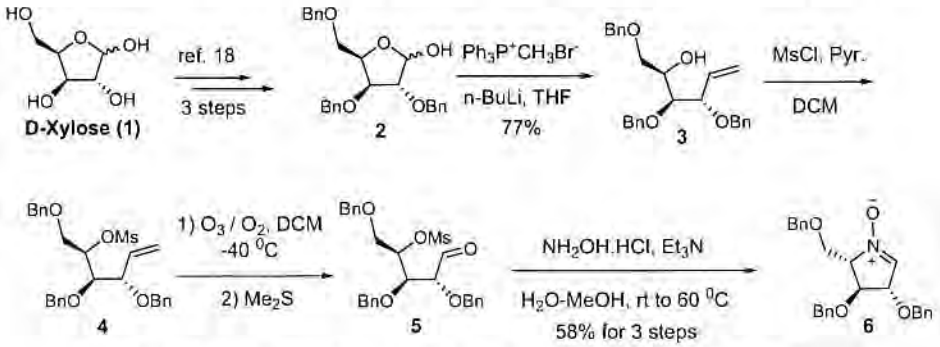
Imino sugars or glycitols ("nitrogen-in-the-ring" analogues of pyranoses and furanoses) are compounds mimicking the structures of monosaccharides, i.e., polyhydroxylated derivatives resulting from replacement of the sugar ring O-atom with a NH-group. Such kind of "nitrogen-in-the-ring" sugar mimics have been frequently isolated from natural sources and are now believed to exist widespreadly in plants and microorganisms. Many iminosugars, either synthetic or naturally occurring, exhibit potent glycosidase inhibitory activities. Since glycosidases are involved in a wide range of important biological processes, iminosugars might have enormous therapeutic potential in many diseases such as viral infection, cancer and diabetes. Such awareness has led to increasing interest and demand for these compounds[1].

The chemical synthesis of iminosuagrs is extensively developed and well-documented in the literature. Among them, methods based on the highly diastereoselective addition of organometallic reagents the polyhydroxylated cyclic nitrones, i.e., introduction of substituents through addition of a nucleophile to a polydroxylated cyclic nitrone is potentially powerful approach[2].

Inspired by the reported methods. we designed the synthetic route for the synthesis of 6. The partially protected sugar 2 derived from D-xylose was treated with methylenetriphenylphosphorane to give the alkene 3 and the resulting secondary alcohol was transformed to *O*-mesylate 4. After ozonolysis of the terminal alkene, the aldehyde 5 with a leaving group was obtained. Treatment of the 4-mesylate-aldehyde 5 with hydroxylamine under basic conditions produced the cyclic nitrone 6 possibly through the formation of a geminal bis-(hydroxylamino)sugar, then cyclisation and subquent elimination of the second hydroxylamine unit. During nitrone formation, although pyridine was inefficient as a base, triethylamine, diethylamine, sodium bicarbonate and sodium carbonate all work well for mediating this process. This synthetic approach possesses obvious merits in that (1) one-pot reactions can be effected from 3 to the final product 6; and (2) the sequence is capable of multi-gram scale synthesis.



Scheme 1 A practical synthesis of polyhydroxylated cyclic nitrones

Starting from cyclic nitrone 6, a number of polyhydroxylated pyrrolidines, such radicamines A and B, homoDMDP, 6-deoxy-homoDMDP, DMDP and 5-*epi*-Hyacinthacine A3 have been synthesized.

References:

1. For reviews about iminosugars, see: (a) Stütz, AE. *Iminosugars as Glycosidase Inhibitors: Nojirimycin and Beyond*; Wiley–VCH: Weinheim, 1999. (b) Asano, N; Nash, RJ; Molyneux, RJ; Fleet, GW. J. *Tetrahedron: Asymmetry* 2000, *11*, 1645–1680. (c) Watson, AA; Fleet, G. WJ; Asano, N.; Molyneux, RJ; Nash, RJ. *Phytochemistry* 2001, *56*, 265–295.

2. For a recent review, see: Revuelta, J; Cicchi, S; Goti, A; Brandi, A. *Synthsis*, 2007, 485-504.

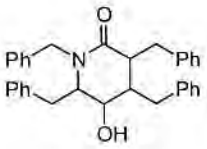
MP134

SYNTHESIS OF SIX- AND SEVEN- MEMBERED LACTAM-BASED HIV PROTEASE INHIBITORS

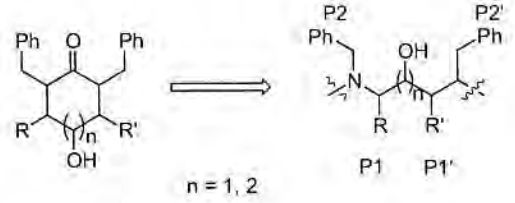
Shazia Zaman and Andrew D. Abell

Department of Chemistry, University of Canterbury, Christchurch, Private Bag 4800 New Zealand

Cyclic lactams such as 1 possess good inhibitory potency against HIV proteas.[1] These nitrogen heterocycles are viewed as cyclic mimics of a straight chain protease inhibitor, with the functional groups around the ring seen as the P1, P1', P2 and P2' binding groups of the inhibitor. To date, very few general synthetic methods of functionalised piperidinones and 1-azapin-2-ones have been observed.[2] Therefore, we have been interested in the development of a general method for the preparation of these compounds.



1

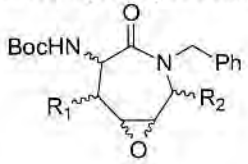


n = 1, 2

Figure 1

We have developed a versatile synthesis of various substituted 1-azepin 2-ones (e.g. 2 and 3) and piperidinones (e.g. 4 and 5). The synthetic sequence involves ring-closing metathesis of a diene amide, followed by either epoxidation or hydroxylation, of the resulting alkene.

2



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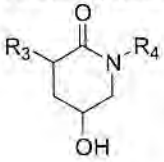

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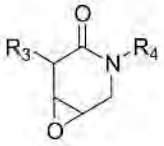

5

R_1 = H, R_2 = H
R_1 = H, R_2 = Ph
R_1 = CH_2Ph, R_2 = H
R_3 = CH_2Ph, R_4 = Cbz

Figure 2

The seven membered lactams were assayed against HIV protease and their inhibitory activity determined.[3] The evaluation of six-membered lactams against HIV Protease is in progress.

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2. Battisini L, Rassu G, Pinna L., Zanardi F, Casiraghi G. *Tet. Asymm.*, 1999, 10, 765-773.
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Tuesday 17th July
Keynote & Plenary Speaker Abstracts

FUNCTIONAL SOFT MATERIALS BY PROGRAMMED MOLECULAR ASSEMBLY

Takuzo Aida and Takanori Fukushima

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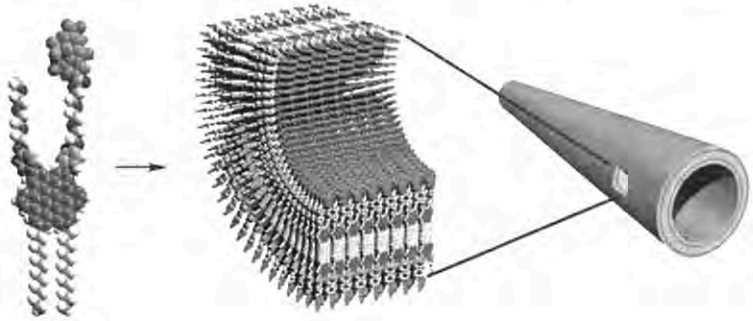
Understanding and utilization of π-electronic conjugation has become of increasing importance in materials sciences, particularly, for targeting molecular electronics, and a variety of molecules and substances, which show interesting optoelectronic properties have recently been reported.

We recently found that bucky gels, prepared by grinding single-walled carbon nanotubes in imidazolium ion-based ionic liquids (1, 2), serve as highly powerful capacitors, and can be applicable to the fabrication of fully plastic actuators by layer-by-layer casting (3). There are many other potential applications (4). Graphitic nanotubes, prepared by self-assembly of an amphiphilic hexa-peri-hexabenzocoronene (5), are also interesting electronically active materials (6). We also succeeded in obtaining a pseudo-crosslinked version of this graphitic nanotube by ADMET-triggered self-assembly of an allyl group-appended new amphiphilic hexa-peri-hexabenzocoronene (7). On the other hand, we have developed photo and redox-mediated covalent stabilization of the graphitic nanotubes (8, 9). Use of a chiral amphiphilic hexa-peri-hexabenzocoronene with stereogenic centres results in the formation of graphitic nanotubes with one-handed helical chirality (10, 11). Water-dispersible graphitic nanotubes and surface-polymerized graphitic coils have also been fabricated (12, 13). The most recent achievement includes the successful fabrication of a photoconductive graphitic nanotube with a coaxial architecture (14).



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(1) Fukushima et al., *Science* **2003**, *300*, 2072. (2) Fukushima et al., *Small* **2006**, *2*, 554. (3) Fukushima et al. *Angew, Chem., Int. Ed.* **2005**, *44*, 2410. (4) Fukushima et al. *Chem. Eur. J. (Concepts)* **2007**, in press. (5) Müllen et al., *Chem. Rev.* **2007**, *107*, 718. (6) Fukushima et al., *Science* **2004**, *304*, 1481. (7) Jin et al., *J. Am. Chem. Soc.*, **2005**, *127*, 10020. (8) Motoyanagi et al., *J. Am. Chem. Soc.* **2006**, *128*, 4220. (9) Motoyanagi et al., *J. Polym. Sci., Part A, Polym. Chem. Ed.* **2006**, *44*, 5120. (10) Jin et al., *Proc. Natl. Acad. Sci., USA* **2005**, *102*, 10801. (11) Yamamoto et al., *Adv. Mater.* **2006**, *18*, 1297. (12) Zhang et al., *J. Am. Chem. Soc.* **2007**, *129*, 719. (13) Yamamoto et al. *J. Am. Chem. Soc.* **2006**, *128*, 14337. (14) Yamamoto et al., *Science* **2006**, *314*, 1761.

A GENERAL AND PRACTICAL SYNTHESIS OF BENZTHIAZOLES

Toshiaki Mase and Takahiro Itoh

Process Research, Preclinical Development, Banyu Pharmaceutical Co., Ltd. Okubo 3, Tsukuba, Ibaraki 300-2611, Japan

Benzazoles are a very important pharmacophoric substructure in drug discovery (1). As part of our ongoing investigation of several drug candidates, we required an efficient and general synthesis of this class of compounds. Condensation of carboxlic acids with 2-aminoaniline, 2-aminothiophenol and 2-aminophenol would be one of the most efficient ways to access benzazoles (1). Buchwald/Hartwig type cross-coupling is a powerful tool for introducing heteroatoms onto aromatic rings related to these compounds. There have been numerous published reports in this field. While there have also been some published reports of the sulphur version of this chemistry, the scope and limitations have not been well defined. Particularly, from industry perspective, no precedent had been reported on cross-coupling reactions with cheaper aryl halides (than aryl iodides) and a way to access bare SH group (2). Therefore, we focused on developing a transition-metal catalyzed cross-coupling of aryl halides with H_2S surrogates. After a great effort, we finally found that the reactions with aryl bromides were smoothly catalyzed by $Pd_2(dba)_3$ using Xantphos as a ligand in the presence of *i*-Pr_2NEt. In the reaction, various aryl bromides were well tolerated to form a wide variety of aryl sulfides (3). Treatment of the resulting surrogates with an acid or a base gave the corresponding arylthiazoles in good yields. 1-Acylamino-2-bromobenzene was successfully transformed to some surrogates, which were deprotected and spontaneously cyclized to 2-methylthiazole (4). In this presentation, this thiazole synthesis including cross-coupling with H_2S surrogates will be highlighted. Application of this methodology for synthesis of a drug candidate (5, 6) will also be presented in this conference.

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(1) (a) Zou B., Yuan Q., Ma D. *Angew. Chem. Int. Ed.* 2007; 46, 2598-2601 and references cited therein. (b) Evindar G., Batey RA. *J. Org. Chem.* 2006; 71, 1802-1808 and references cited therein. (c) Rudawar S., Kondaskar A., Chakraborti AK. *Synthesis*, 2005; 15, 2521-2526 and references cited therein.

(2) Arnould JC., Didelot MD., Cadilhac C., Pasquet MJ. *Tetrahedron Lett.*, 1996; 37, 4523-4524.

(3) (a) Itoh T., Mase T. *Org. Lett*, 2004; 6, 4587-4590. (b) Murata M., Buchwald SL. *Tetrahedron*, 2004; 60, 7397-7403. (c) Fernandez-Rodriguez MA., Shen Q., Hartwig JF. *J. Am. Chem. Soc.*, 2006; 128, 2180-2181. (d) Mispelaere-Canivet C., Spindler J-F., Perrio S., Beslin P. *Tetrahedron*, 2005; 61, 5253-5259.

(4) To be submitted.

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(6) (a) Iida T., Satoh H., Maeda K., Yamamoto Y., Asakawa K., Sawada N., Wada T., Kadowaki C., Itoh T., Mase T., Weissman SA., Tschaen DM., Krska S., Volante RP. *J. Org. Chem.*, 2005; 70, 9222-9229. (b) Itoh T., Sato K., Mase T. *Adv. Synth. Catal.*, 2004; 346, 1859-1867. (c)Itoh T., Mase T. *Tetrahedron Lett.*, 2005; 46, 3573-3577. (d) Itoh T., Mase T. *J. Synth. Org. Chem. Jpn.*, 2007; in press.

THE SYNTHESIS OF NOVEL DRUG CANDIDATES

David M. Tschaen

Merck Research Labs

Department of Process Research

Pharmaceutical research and development is a highly competitive global industry which is under increasing pressure to discover and develop new medicines more efficiently and cost effectively. In addition, the rapid and economical synthesis of new drug candidates is becoming increasingly more challenging in part because many novel pharmaceutical targets are reasonably complex structures. Novel drug candidates often contain interesting heterocyclic components as well as challenging asymmetric centers. Therefore, designing and developing efficient asymmetric routes to prepare these novel pharmaceuticals requires the discovery and application of the latest breakthroughs in synthetic methodology. The development of practical and efficient asymmetric approaches to some novel drug candidates will be described.

BIOMIMETIC FOULING CONTROL: DEVELOPMENT OF NOVEL ANTIMICROBIAL AGENTS

Naresh Kumar[1,2]

[1]*School of Chemistry, University of New South Wales, Sydney NSW 2052, Australia*

[2]*Biosignal Ltd, Australian Technology Park, Eveleigh NSW 1430, Australia*

Email: n.kumar@unsw.edu.au

The emergence of multi-drug resistance in common human pathogens has highlighted the need to identify new anti-microbials and moreover, the need to develop novel classes of anti-microbials for the treatment of human disease. It is now increasingly apparent that many bacteria control the expression of virulence factors in a density-dependent fashion and coordinate this behaviour through the use of chemical cues or signals in processes known as microbial cell-cell signalling. Our efforts to develop novel antagonists of bacterial signalling pathways based on 3-butyl-4-halo-5-halomethylene-2(5H)-furanones, a class of marine natural products from the red alga, *Delisea pulchra*, will be highlighted.

Tuesday 17th July
Mathews Theatre A
Invited Lectures & Contributed Oral Presentations
1:30pm-3:00pm

NOVEL HETEROCYCLIC RADIOPHARMACEUTICALS FOR IMAGING CANCER, NEURODEGENERATION AND INFLAMMATION

Andrew Katsifis, C. Fookes, T. Pham, F. Mattner, X. Liu, I. Greguric, P. Berghofer.

Radiopharmaceuticals Research Institute, ANSTO. New Illawarra Rd, Lucas Heights 2234, Sydney, NSW Australia.

The visualisation, characterisation and measurement of biological processes at the molecular and cellular levels in living systems using radiolabelled probes is having an enormous impact in our understanding of basic disease processes and is significantly contributing to "personalised health care" around the globe. These advances have largely been driven by significant advances in imaging technologies such as positron emission tomography (PET), and modern molecular radiopharmaceuticals based on carbon-11, fluorine-18 and the radioiodines, allowing the imaging and study of specific biochemical pathways, enzymes and receptors.

One such family of receptors are the "peripheral and central - benzodiazepine receptors" or PBR and CBR respectively. The CBR are primarily located in the CNS are associated with the $GABA_A$ ion channels and have long been characterised by the well known benzodiazepine drugs diazepam, flumazenil and triazolam. The PBR in contrast, are primarily located on the outer mitochondrial membranes in cells and found in peripheral tissues such as the adrenals, testes, ovaries heart, and kidney and in very low concentrations in the brain. The PBR have been largely characterised by the radiolabelled isoquinoline ligand PK 11195. More significantly a number of disease states such as neurodegeneration, inflammation and cancer have been characterised by alterations in the density of these binding sites in various tissue. Imaging and measuring these receptor changes allows the monitoring of disease progression as well as the follow-up of potential treatments.

Our group has developed novel high affinity and selective heterocyclic molecules based on the imidazopyridine, imidazopyridazine, pyrazolopyrimidine and indolglyoxylamide chemical skeletons which target the PBR. Several of these molecules have been radiolabelled with the short lived radionuclides carbon-11, fluorine-18 or Iodine-123 and evaluated in animal models of inflammation, neurodegeneration as well as in cancer. Similarly, drugs such as flumazenil have also been radiolabelled with both carbon-11 and fluorine-18 to study disorders in the CNS based on altered CBR/GABA function such as epilepsy. The synthesis, radiolabelling, biological evaluation and imaging of selected molecules in animal models of disease using the micro-PET/CT and micro-SPECT/CT imaging modalities will be presented.

References

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TOTAL SYNTHESIS OF THE POTENT ANTICANCER 1,4-DIOXANES (–)-EPISILVESTROL AND (–)-SILVESTROL

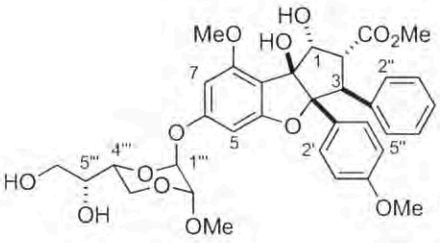
Mariana El Sous,[1] Mui Ling Khoo,[1] Georgina Holloway,[2] David Owen,[3] Peter J. Scammells[2] and Mark A. Rizzacasa*[1]

[1]*School of Chemistry, The Bio21 Molecular Science and Biotechnology Institute, The University of Melbourne, Victoria 3010, Australia.*

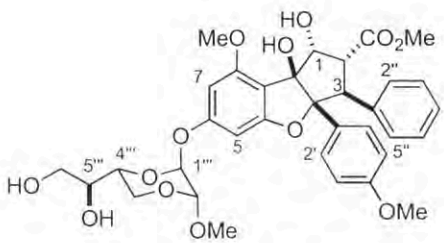
[2]*Department of Medicinal Chemistry, Victorian College of Pharmacy, Monash University, Victoria 3010, Australia.*

[3]*Cerylid Biosciences, Melbourne, Australia.*

Extracts of the bark of the woody South East Asian shrub *Aglaia leptantha*, showed potent cytotoxic activity which was attributed to two new molecules 1 and 2.[1] Compounds 1 and 2 are related as diastereoisomers (epimers at 5‴) that contain a common cyclopenta[*b*]-benzofuran core as well as an unprecedented 1,4-dioxanyloxy 'pseudosugar' substituent.[3] In addition, two metabolites, named silvestrol and episilvestrol were isolated from *Aglaia foveolata* by Kinghorn and co-workers and found to be identical to 1 and 2 respectively.[2] Both silvestrol (1) and episilvestrol (2) showed comparable potent cytotoxic activity against several human tumour cell lines including lung, prostate and breast cancer with IC_{50} values ranging from 1-7 nM.[1,2] Unfortunately, the paucity of both 1 and 2 from the natural source precludes isolation as a sufficient supply of these important compounds. Therefore, an efficient chemical synthesis is an attractive alternative for accessing quantities of 1 or 2 as well as analogues for further biological evaluation. This lecture will describe the total synthesis of (–)-episilvestrol (2) and (–)-silvestrol (1) from common simple precursors.



1 *Silvestrol*



2 *Episilvestrol*

References:

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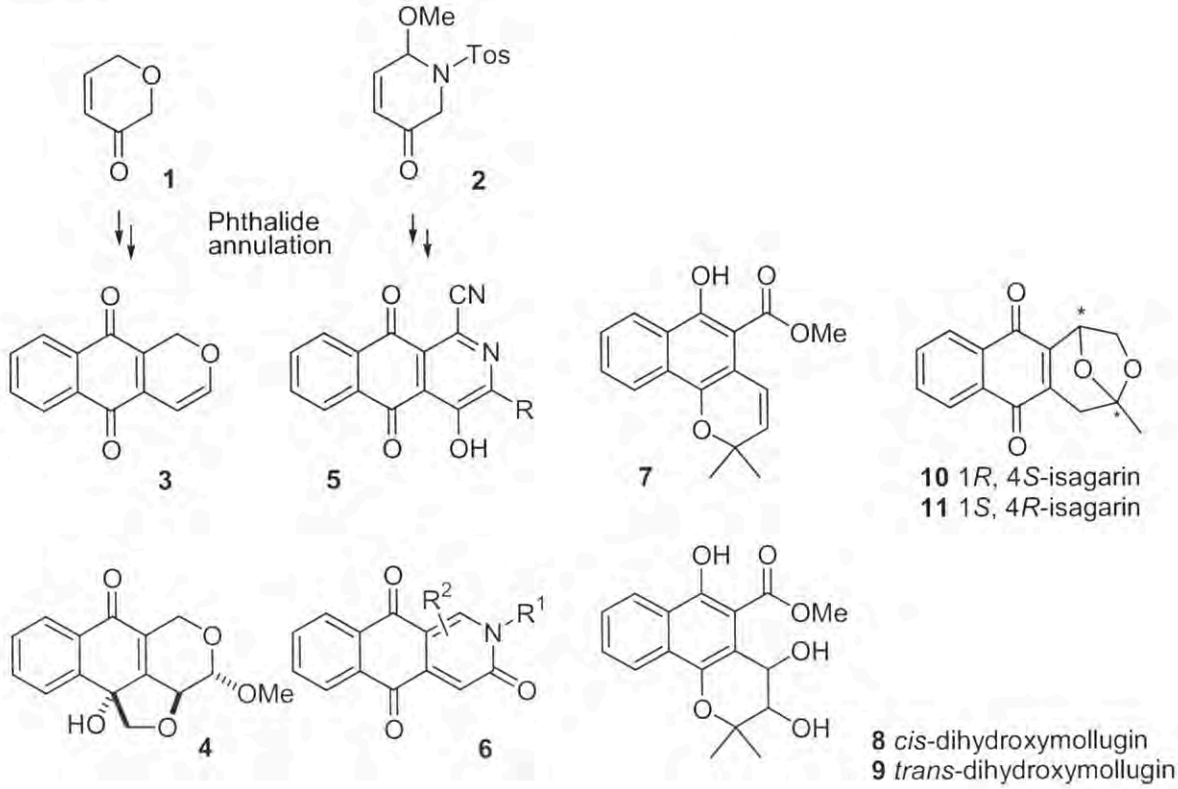
SYNTHESIS OF NATURAL PYRANONAPHTHOQUINONES AND RELATED *N*-CONTAINING NATURAL PRODUCTS

Sven Claessens,[1] Jan Jacobs,[1] Pascal Habonimana,[1] Kris Huygen,[2] Norbert De Kimpe[1]*

[1]*Department of Organic Chemistry, Faculty of Bioscience Engineering, Ghent University, Coupure links 653, B-9000 Ghent, Belgium*

[2]*Pasteur Institute, Engelandstraat 642, B-1180 Brussels, Belgium*

Pentalongin 3 is the active principle isolated from the roots of the Central East African medicinal plant *Pentas longiflora*. Pentalongin 3 reveals the basic skeleton of 3,4-dehydropyranonaphthoquinones which form an important family of quinone compounds. Pentalongin 3 was synthesized by a phthalide annulation using a novel enone receptor 1 and this methodology was extended towards the corresponding nitrogen analogues 2. In the case of annulation with piperidone derivative 2, 2-aza-1-cyano-4-hydroxyanthraquinones 5 were formed. These 2-azaanthraquinones 5 and benzo[*g*]isoquinoline-triones 6 are aza-bioisosteres of pentalongin 3. Pentalongin 3 turned out to be a fairly unstable natural product, the instability of which was investigated in alcoholic media. This study led to the isolation of, among others, tetracyclic compound 4. The identity of this compound with a novel heterocyclic skeleton was confirmed by synthesis in order to unravel the degradation mechanism.



Mollugin 7, together with *cis*- and *trans*-dihydroxylated analogues 8 and 9 have been isolated from *Pentas longiflora* as well as from other rubiaceous herbs which are often used in Chinese folk medicine. Synthetic routes to these important natural products 7, 8 and 9 are presented. 1*R*,4*S*-Isagarin 10 and 1*S*,4*R*-isagarin 11, which display a novel tetracyclic skeleton, were synthesized by the use of the Sharpless-protocol for asymmetric dihydroxylation. Testing of the obtained compounds for their activity against *Mycobacterium tuberculosis* showed promising results.

APPLICATION OF IMINIUM-ACTIVATION TECHNOLOGIES TOWARDS THE TOTAL SYNTHESIS OF FRONDOSIN B

Maud Reiter, Sandra Lee, David W. C. MacMillan.

Princeton University, Frick Laboratory, Princeton, NJ 08544 USA

We have demonstrated that the LUMO-lowering activation of α,β-unsaturated aldehydes *via* the reversible formation of iminium ions is a valuable platform for the development of enantioselective 1,4-conjugate addition reactions of a range of electron-rich nucleophiles such as aniline, pyrrole and indole derivatives. Herein, we expand the scope of this reaction towards the addition of less electron-rich substrates by employing activated organoborate derivates as nucleophiles, hereby mimicking a Petasis boronic acid-Mannich type reaction (Figure 1).[1]

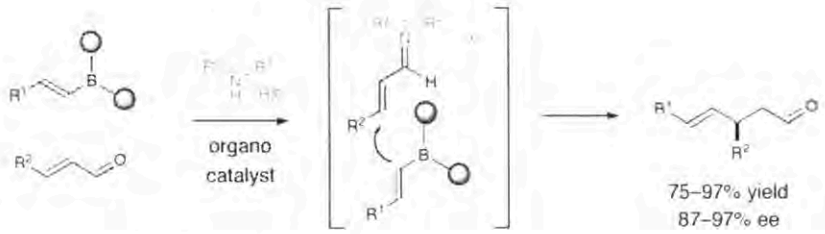


Figure 1: 1,4-Addition of potassium trifluoroborate complexes to α,β-unsaturated aldehydes.

Further developments of this new methodology were explored towards the total synthesis of natural product Frondosin B, which was isolated from the sponge *Dysidea frondosa* in 1997.[2] This natural product has been found to inhibit the binding of interleukin-8 (IL-8) to its receptors in low micromolar range. We have successfully completed a five-step total synthesis of Frondosin B, featuring as a key step the organocatalytic conjugate addition of a potassium 2-(5-methoxybenzofuranyl) trifluroborate salt substrate (Figure 2).

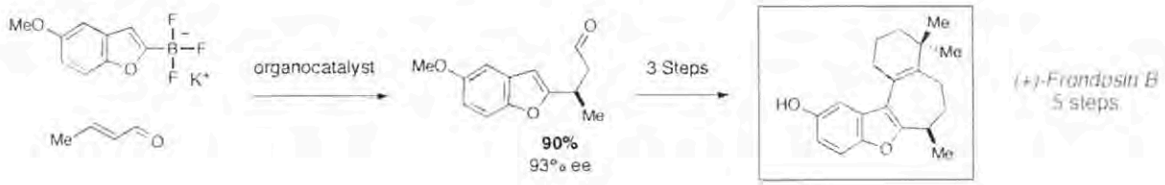


Figure 2: Five-step Synthesis of Frondosin B.

Frondosin B has previously been synthesized by both Danishefsky *et al.*, as well as by Trauner *et al.* in over 17 steps.[3] The absolute configuration of Frondosin B was assigned differently by both research groups. X-ray crystallography data of one of our synthetic intermediates have allowed us to irrefutably prove the absolute configuration of Frondosin B.

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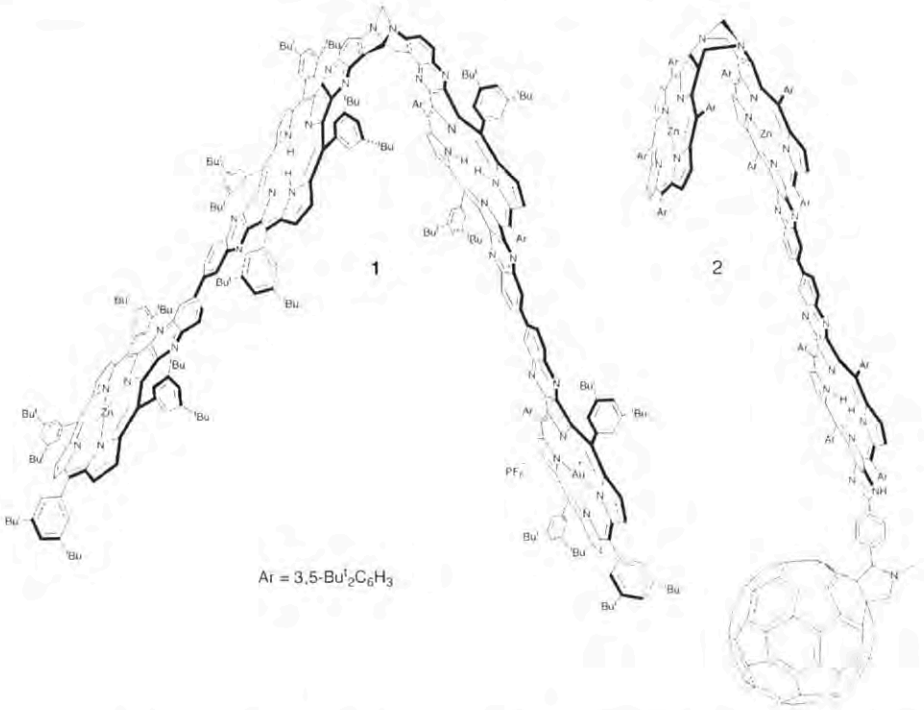
3. a) Danishefsky, SJ; Inoue, M; Carson, MW; Frontier, AJ, *J. Am. Chem. Soc.* 2001, *123*, 1878-1889; b) Hughes, CC; Trauner, D. *Angew. Chem. Int. Ed.* 2002, *41*, 1569-1572.

Tuesday 17th July
Mathews Theatre B
Invited Lectures & Contributed Oral Presentations
1:30pm – 3:00pm

PORPHYRIN-BASED COMPOUNDS THAT MIMIC ASPECTS OF PHOTOSYNTHETIC REACTION CENTRES

Maxwell J. Crossley, Paul J. Sintic, Iain M. Blake, Peter R. Brotherhood, and James A. McDonald
School of Chemistry, The University of Sydney, NSW 2006, Australia

The covalently-linked porphyrin tetrad **1** is the closest mimic yet reported for the natural photosynthetic reaction centres (PRC's).[1] Photoexcitation of the zinc(II) porphyrin in **1** ultimately leads by a multistep process to a final giant charge-separated state spanning 50Å with a lifetime of 59 microseconds in benzonitrile. Binding chloride ion to the zinc(II) leads to a larger redox driving force and increases the lifetime of the charge-separated state to 2.1 milliseconds.



As good as tetrad **1** is as a distance and orientation mimic of the PRC's, it has several deficiencies; the 'special pair' of porphyrins are not metalated and are too far apart and thus are unable to delocalise the cation-radical character that these chromophores share in natural PRC's, and **1** lacks an electron acceptor to mimic the quinones and iron-sulfur complexes of natural systems. We have synthesised the tetrad **2** that has shorter linkers between the 'special pair' and a C60 acceptor to overcome these deficiencies, and this work is described in this presentation.

Reference

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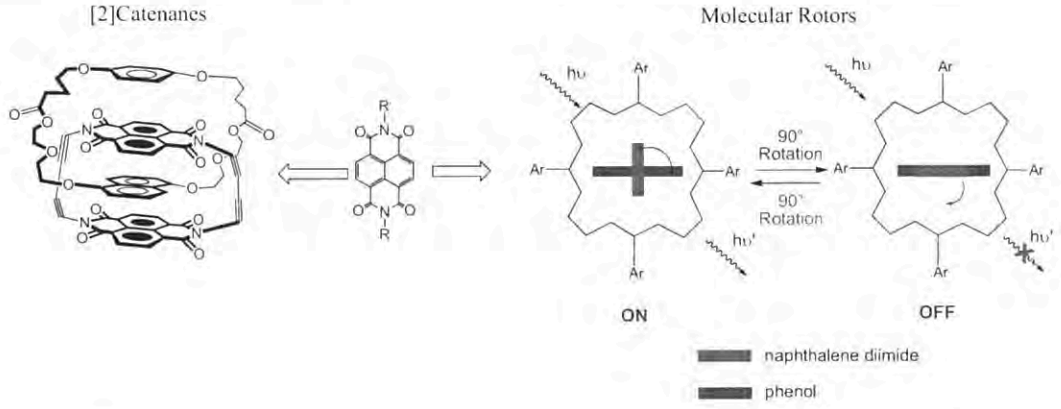
ON THE CHEMISTRY OF 1,4,5,8-NAPHTHALENEDIIMIDES

Steven J. Langford

School of Chemistry, Monash University, Clayton Vic 3800, Australia

Naphthalenediimides have found popularity in the latter half of the 20th century and due, in part, to the pioneering work of Vollmann in the early 1930's.[1] This presentation describes in the chemistry and physical properties of naphthalenediimides and explores their application in the field of supramolecular science. It begins with a discussion of the methods of syntheses and the electronic and spectroscopic properties of 1,4,5,8-naphthalenediimides,[2] and their core substituted analogues, and places these in the context of an ideal functioning component from which to develop molecular devices and machines. Three aspects of supramolecular design will be covered, mechanically-interlocked molecules,[3] a new paradigm for the generation of charge separation through photoinduced electron transfer[4] and a description of a novel molecular rotor for probing nano-environments.[5]



References:

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3. Fallon, GD, Lee, MA-P, Langford, SJ and Nichols PJ. *Org. Lett,* 2004, 6, 655-658.

4. (a) Ghiggino, KP, Hutchison JA, Langford SJ, Latter, MJ, Lee MA-P and Takezaki, M. *Aust. J. Chem,* 2006, 59, 179-185.

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COLORIMETRIC RECOGNITION OF SPERMIDINE AND SPERMINE BASED ON PHENOLPHTHALEIN DERIVATIVES

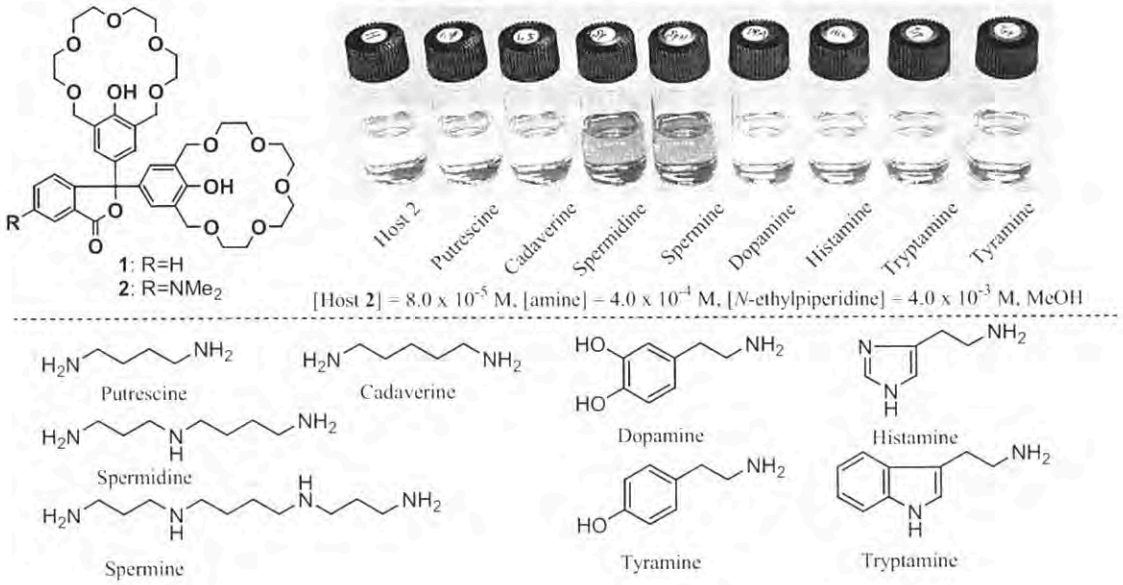
Kazunori Tsubaki, Daisuke Tanima, Takeo Kawabata

Institute for Chemical Research, Kyoto University, Uji, Kyoto 611-0011, Japan.

The design and construction of chemosensors for recognizing biologically important small molecules have received considerable attention in recent years. Recently, we have reported the ditopic receptor 1 based on phenolphthalein (well-known pH indicator), which illustrated dramatic coloration toward linear diamine and/or triamine systems via hydrogen bondings through formation of bridged-type complex in protic solvents such as methanol.

On the other hand, the polyamines inclusively indicate the organic compounds with two or more amino groups, and spermidine, spermine, putrescine, and cadaverine are known as polyamines in vivo. The polyamines are important physiologically active substances and deeply related to the differentiation and the proliferation of the cell. Especially, the concentration of both spermidine and spermine are increasing in the cancer cell, diacetylspermidine in the urine is used as a tumour marker. However, the metrology for determination of concentration of polyamines used by clinical is complicated, so the development of a simple and useful polyamine detection reagent is desired

In this presentation, we wish to report the development of high sensitive receptor 2 having *N,N*-dimethylamino group on *m*-position of carbonyl group. Compare to receptor 1, receptor 2 shows ten times sensitive to spermidine and spermine in methanol. Furthermore, receptor 2 can strictly recognize spermidine and spermine among other polyamines and amines in vivo.



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(a)Fuji K. Tsubaki K. Tanaka K. Hayashi N. Otsubo T. Kinoshita T. *J. Am. Chem. Soc.*, 1999, 121, 3807-3808. (b) Tsubaki K. Hayashi N. Nuruzzaman M. Kusumoto T. Fuji K. *Org. Lett.*, 2001, 3, 4067-4069. (c) Tsubaki, K. Nuruzzaman, M. Kusumoto, T. Hayashi, N. Wang, BG. Fuji K. *Org. Lett.*, 2001, 3, 4071-4073. (d) Tsubaki K. Kusumoto T. Hayashi N. Nuruzzaman M. Fuji. K. *Org. Lett.*, 2002, 4, 2313-2316. (e) Tsubaki K. Tanima, D. Nuruzzaman, M. Kusumoto T. Fuji K. Kawabata T. *J. Org. Chem.*, 2005, 70, 4609-4616. (f) Tsubaki K. Tanima D. Sasamori T. Tokitoh N. Kawabata T. *Tetrahedron Lett.* 2007, 48, 2135-2138.

TRÖGER'S BASE ANALOGUES AS NLO CHROMOPHORES

M. Delower H. Bhuiyan,[a] Thomas Bredow,[b] Damian Moran[a] and Andrew C. Try[a]

[a] *Department of Chemistry and Biomolecular Sciences, Macquarie University 2109, Sydney, Australia.* [b] *Theoretische Chemie, Universität Bonn, 53115 Bonn, Germany*
andrew.try@mq.edu.au

Analogues of Tröger's base (R = CH_3 at the 2- and 8- positions in Figure 1) bearing electron-withdrawing groups have historically been difficult to prepare as their formation involves the acid-catalysed condensation of formaldehyde equivalents with substituted anilines. Recently, however, several reagent combinations have been found to result in the synthesis of halogen,[1,2] nitro[2,3] and ester substituted Tröger's base analogues.[2,4-6]

Tröger's base analogues substituted with electron-withdrawing groups satisfy the basic criteria for organic molecules to exhibit non-linear optical (NLO) activity; electron-donor and electron-acceptor groups connected through a conjugated framework. We wish to report our preliminary work in this area, with the synthesis of a range of new Tröger's base analogues, as exemplified in Figure 1, and the results of a computational study aimed at predicting some important properties of these compounds.

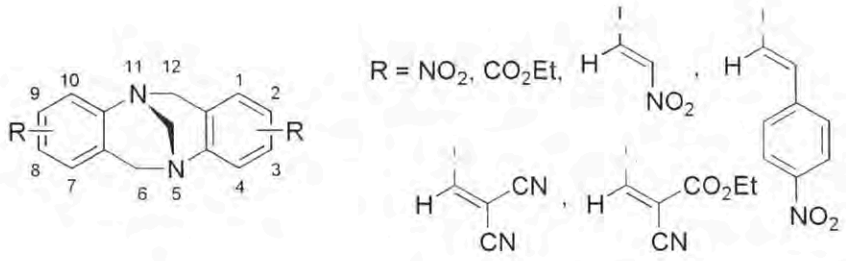

Figure 1

References:
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(3) Mederski, W. W. K. R.; Baumgarth, M.; Germann, M.; Kux, D.; Weitzel, T. *Tetrahedron Lett.* 2003; 44, 2133-2136.
(4) Goswami, S.; Ghosh, K.; Dasgupta, S. *J. Org. Chem.* 2000; 65, 1907-1914.
(5) Faroughi, M.; Try, A. C.; Turner, P. *Acta. Cryst.* 2006; E62, o3479-o3480.
(6) Bhuiyan, M. D. H.; Try, A. C.; Klepetko, J.; Turner, P. *Acta. Cryst.* 2006; E62, o4887-o4888.

Tuesday 17th July
Mathews Theatre C
Invited Lectures & Contributed Oral Presentations
1:30pm-3:00pm

HETEROCYCLE SYNTHESIS VIA RADICAL REACTION

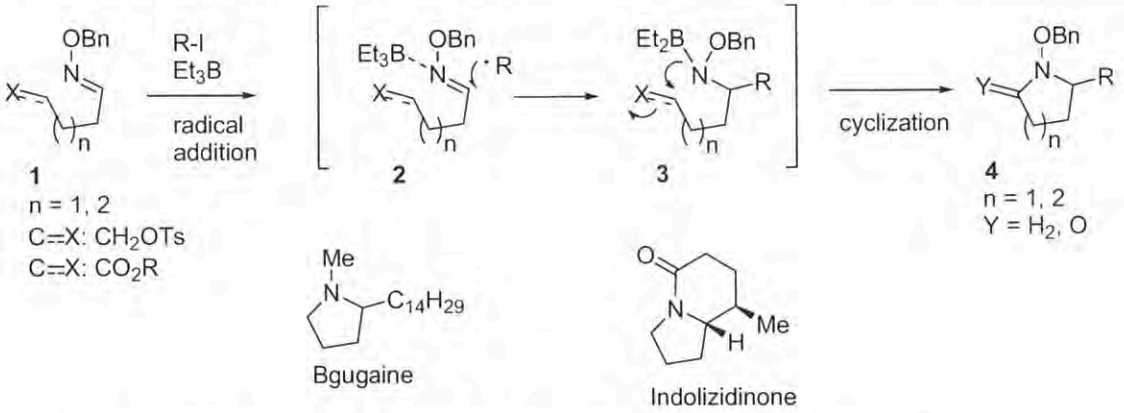
Takeaki Naito

Medicinal Chemistry Laboratory, Kobe Pharmaceutical University
4-19-1, Motoyamakita, Higashinada, Kobe 658-8558, Japan

During the course of our recent study on radical addition to imines,[1,2] we developed novel synthetic method for the preparation of nitrogen containing heterocycles via the route involving domino type radical addition-cyclization reaction of oxime ethers.

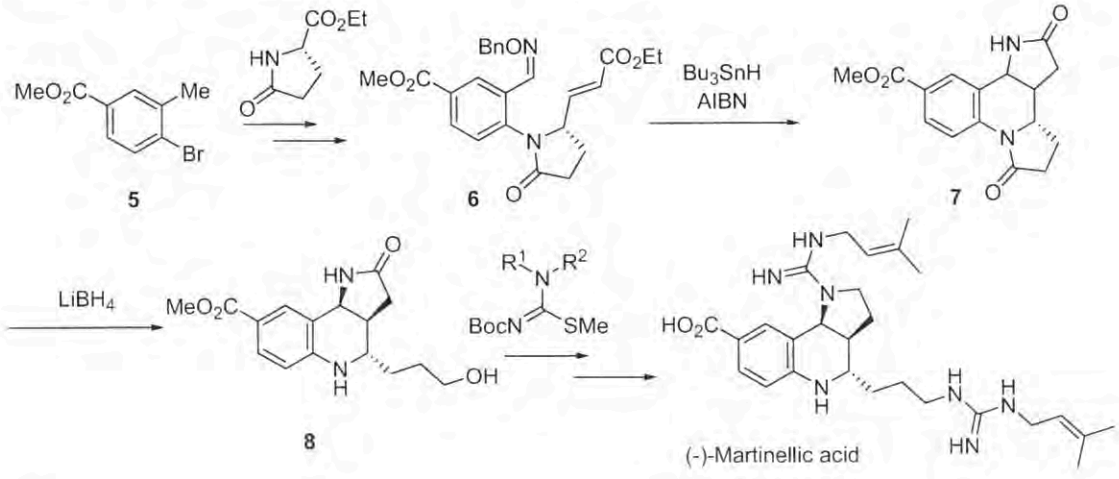
1. Radical Addition-Cyclization and Heterocycle Synthesis

Oxime ethers 1 carrying a leaving group underwent alkyl radical addition to form alkylated amino boranes 3 which took place intramolecular cyclization to form pyrrolidines, piperidines, and their corresponding lactams 4. The domino reaction was successfully applied to the synthesis of Bgugaine and indolizidinone.



2. Total Synthesis of (-)-Martinellic Acid via Radical Addition-Cyclization-Elimination[3]

Radical addition-cyclization-elimination reaction of oxime ether carrying α,β-unsaturated ester 6 proceeded smoothly to give tetracyclic pyrroloquinoline skeleton 7 which is a core structure of Martinelline alkaloids. Transformation of the functional groups including introduction of the guanidine moiety completed the total synthesis of (-)-martinellic acid.



References:

1. Miyabe H., Ueda M., Naito T., *Synlett*, 2004; 1140-1157.

2. Ueda M., Miyabe H., Sugino H., Miyata O., Naito T., *Angew. Chem. Int. Ed.*, 2005; *44*, 6190-6193.
3. Miyata O., Shirai A., Yoshino S., Takeda Y., Sugiura M., Naito T., *Synlett*, 2006; 893-896.

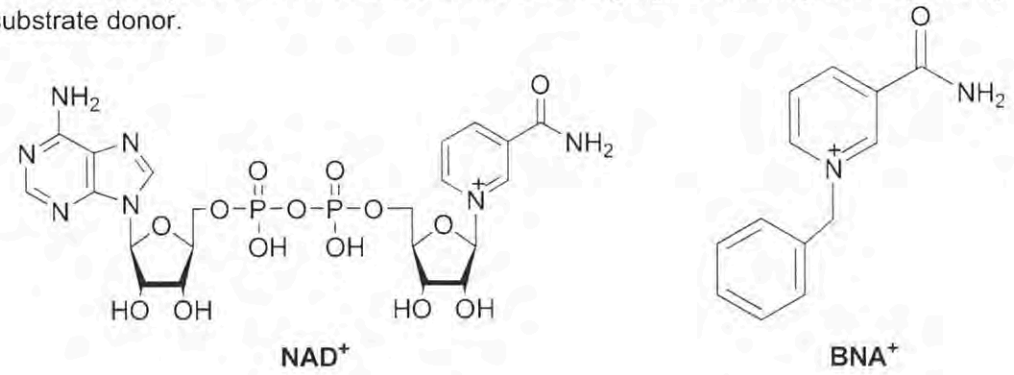
Mathews Theatre C – Contributed Oral Presentations 2:00pm – 3:00pm

PHOTOCATALYTIC REDUCTION OF NAD^+

Palli Thordarson, Danial M Stocks, Maxwell J Crossley, Gabrielle de Wit and Shiva Prasad

School of Chemistry, The University of Sydney 2006, Sydney NSW, Australia

Nicotinamide adenine dinucleotide (**NAD^+**) and its reduced form NADH play a crucial role in biological systems as redox coenzymes.[1] In enzymatic reactions involving the reduction of a substrate, NADH acts as a reducing agent providing a hydride ion or two electrons and a proton to the resulting substrate. Alternatively, NAD^+ can be used as an oxidizing agent whereby it accepts a hydride ion from a substrate donor.



NAD^+ **BNA^+**

Recently it has been demonstrated that tin(IV) porphyrins are effective and mild photocatalysts for the reduction of various mono- and multivalent metal ions.[2] Inspired by this work we have targeted the use of tin(IV) porphyrins as photocatalysts for the *in vitro* reduction of NAD^+. A number of key results have been obtained in our laboratory regarding the preparation of water-soluble tin(IV) metalloporphyrins and their redox capabilities in the presence of NAD^+ and benzylnicotinamide (**BNA^+**), an analogue of NAD^+, with a sacrificial electron donor such as triethanolamine (TEA) or ascorbic acid (Figure 1).

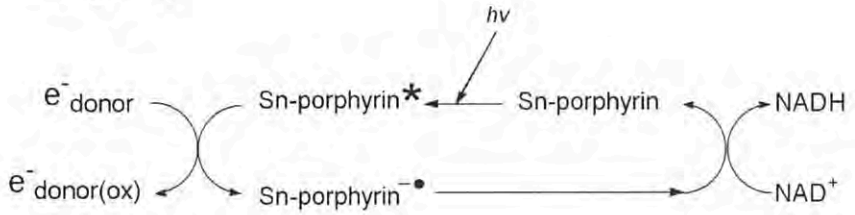


Figure 1. Schematic representation of our photocatalytic system.

Our studies on the photocatalytic reduction of BNA and NAD+ will present here. These studies and our current work on chemically modified NAD^+ will be presented in this paper. We hope to show that this approach is viable for the regeneration of NADH which could become very useful in NADH-dependent processes in enzymatic synthesis and biosensors.

References:

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2. Song Y, Yang, Y, Medforth, CJ, Pereira, E, Singh, AK, Xu, H, Jiang, Y, Brinker, CJ, van Swol, F, Shelnutt, JA. J. *Am. Chem. Soc.*, 2004; 126, 635-645.

SYNTHETIC ROUTES TO NOVEL BISBENZIMIDAZOLES AS POTENTIAL DRUG CANDIDATES

A. Mayence,[1] A. Pietka,[2] J.J. Vanden Eynde,[2] T. Huang,[1] E. Anders[3]

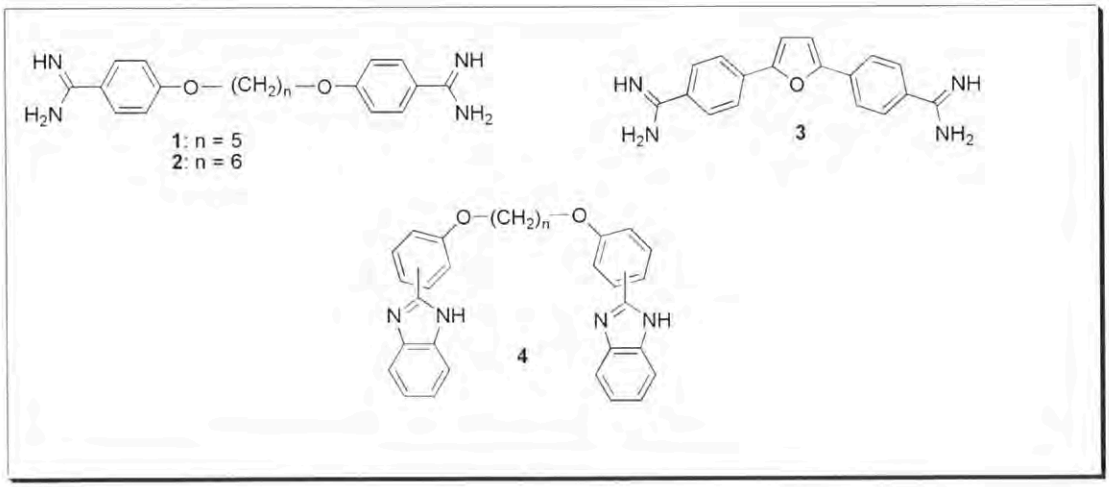
[1] *Xavier University of Louisiana, College of pharmacy, New Orleans, LA 70125, USA*

[2] *University of Mons-Hainaut, Organic chemistry department, B-7000 Mons, Belgium*

[3] *Friedrich-Schiller-University, Institute for organic and macromolecular chemistry, D-07743 Jena, Germany*

Pentamidine (1), hexamidine (2), furamidine (3), and other aromatic diamidines are efficient or potential drugs for the treatment of *Pneumocystis carinii* pneumonia, trypanosomiasis, leishmaniasis, and other infectious diseases [1-4]. However those compounds are characterized by important limitations, *e.g.* poor bioavailability and severe side effects, sometimes attributed to the pharmacophores themselves.

In this study, we report the preparation of novel analogs of those derivatives in which the amidine functions have been replaced by benzimidazole moieties. The target compounds (4), [alpha,omega-alkanediylbis(oxyphenylene)]bis-1*H*-benzimidazoles, have been synthesized from alpha,omega-dibromoalkanes and hydroxybenzaldehydes, followed by an oxidative reaction with a 1,2-phenylenediamine. The synthetic routes used to form the heterocyclic ring systems will be presented and preliminary pharmacological data will be disclosed.



References:

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[3]. Cushion M.T., Walzer P.D., Ashbaugh A., Rebholz S., Brubaker R., Vanden Eynde J.J., Mayence A., Huang T.L. *Antimicrob. Agents Chemother.* 2006; 50, 2337-2343.
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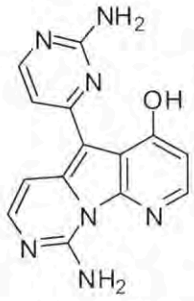
DEVELOPMENT OF PYRROLOPYRIMIDINES AS INHIBITORS OF ATP-BINDING PROTEINS

Jonathan C. Morris

School of Chemistry & Physics, University of Adelaide, Australia

The variolins are a novel class of marine alkaloids isolated from the rare Antarctic sponge *Kirkpatrickia varialosa*. All of the variolins contain a pyridopyrrolopyrimidine ring system, with variolin B being the most biologically active. Initial biological studies have established that variolin B has potential as an anti-cancer drug due to its potent ability to inhibit the cyclin-dependent kinases.[1] Moreover, it has also been identified as a potent inhibitor of *Brugia malayi* asparaginyl-tRNA synthetase using a ligand docking and screening program.[2] Brugia malayi infection causes lymphatic filariasis (elephantitis), an insect-borne disease that has infected an estimated 200 million people worldwide. With the total synthesis of variolin B already established[3] by the Morris group, efforts are now focussed on developing the pharmaceutical potential of the pyrrolopyrimidine scaffold.



Variolin B

References:

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Tuesday 17th July
Mathews Theatre D
Invited Lectures & Contributed Oral Presentations
1:30pm-3:00pm

THE USE OF SULTINES IN THE ASYMMETRIC SYNTHESIS OF POLYPROPIONATE ANTIBIOTICS

Pierre Vogel

laboratoire de glycochimie et de synthèse asymétrique, Swiss Federal Institute of Technology (EPFL), CH-1015 Lausanne, Switzerland ;
José Angel Sordo, *Departamento de Química Física y Analítica, Universidad de Oviedo, Spain*

Although sulfur dioxide (SO_2) is one of the major natural and man-made air pollutant and that burning of sulfur, which generates SO_2, has been used for more than 8000 years to sanitize containers of food and beverages, the organic chemistry of SO_2 is today quite limited in scope. Applying high level quantum calculations, we intend to understand newly discovered reactions and reaction cascades involving SO_2. These studies have led us to invent new synthetic procedures of high potential for material sciences and medicinal chemistry. Our studies are also pertinent to acid rain and smog formation. They help in the interpretation of experimental data (thermodynamics, kinetics, isotope effects) in connection with the ene-reaction, the cheletropic and the hetero-Diels-Alder additions of SO_2. We are studying also the catalysis of these reactions and of others involving polysulfone polymers[1]. The project establishes a fruitful synergy between experience (EPFL) and theory (Oviedo). In this presentation we shall illustrate the power of our recently discovered reaction cascades based on pericyclic reactions of SO_2 to the efficient asymmetric synthesis of complicated antibiotics such as Rifamycin S [2], Apoptolidin [3] and Baconipyrones [4]. We shall present also new sulfur dioxide mediated one-pot, three and four-component synthesis of polyfunctional sulfonamides, sulfonic esters and sulfones (combinatorial chemistry) [5] and the invention of new strategies for polyols semi-protection and protection using silyl methallylsulfinates for the neutral silylation of alcohols [6].

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REACTIONS OF 2H-1,2,3-DIAZAPHOSPHOLES WITH BIFUNCTIONAL NUCLEOPHILIC REAGENTS: THEORETICAL AND EXPERIMENTAL INVESTIGATION

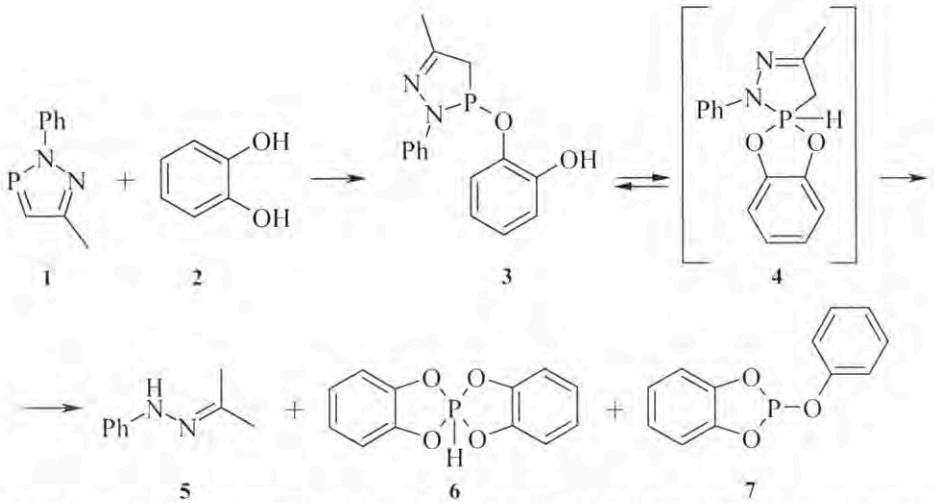
N.G.Khusainov, *M.A.Khusainov, O.A.Mostovaya, *Yu.A.Galyametdinov, S.A.Slivko, R.A.Cherkasov

Kazan State University, Kremlevskaya str.18, Kazan, 420008, Russia

1 **Kazan State Technological University, K.Marks str. 68, Kazan, 420015, Russia*

We have found (by kinetic ^{31}P NMR spectroscopy) that the reaction of the hetercyclic two-coordinated - 2-acetyl-5-methyl-2H-1,2,3-diazaphosphole with *(rac)*butane-2,3-diol at temperature below 0°C leads to formation of 1,2,3-diazaphospholene and asymmetrical hydrospirophosphorane containing both diazaphospholene and dioxaphospholane ring system. Then its interconversion results in fragmentation of the diazaphospholene ring in these compounds with the formation of the symmetrical hydrospirotetraoxaphosphorane, β-hydroxyphosphite, hydrazone and symmetrical bisphosphite as the main products [1]. Termodynamical stability of all these reaction members was analysed by calculation using methods of quantum chemistry (PM3 and HF/6-31G(d,p) methods) for the first time. Instability of the hydrospirophosphorane and the 1,2,3-diazaphospholene is confirmed by quantum chemical calculations. On the basis of thermodynamical characteristics initialy formed products are less expedient in comparison with symmetrical hydrospirotetraoxaphosphorane, its tautomer and symmetrical bisphosphite. Calculations confirm that tautomeric equilibrium in tri- and penta-coordinated phosphorus is shifted towards the hydrospirophosphorane. Response mechanism as nucleophilic 1,2-addition of diol to P=C bond was inferred from preliminary calculation and analysis of charge density in atoms of reactive center. Oxyorganical group attacks atom of two-coordinated phosphorus regioselectively with increasing in phosphorus coordination.

The reaction of 5-methyl-2-phenyl-2H-1,2,3- diazaphosphole **1** with catechol **2** furnishes a mixture of tautomeric 1,2,3-diazaphospholene **3** and asymmetric hydrospirophosphorane **4.** At increasing temperature fill room temperature the **3** and **4** adducts undergo fragmentation into phenylhydrazone acetone **5**, symmetric hydrospirotetraoxaphosphorane **6** and phosphite **7** .



On the analogy the reaction of 2-acetyl-5-methyl-2H-1,2,3-diazaphosphole and aminoethanol proceed with the participation of both proton containing functionalic groups of nucleophilic reagent but of advantage with the formation of the O-functionalized products.

The reaction of 2-acetyl-5-methyl-2H-1,2,3-diazaphosphole with diaminoethan leads to formation of the nonsubstituted by nitrogen atom 5-methyl-2H-1,2,3-diazaphosphole - the hetercyclic two-coordinated phosphorus derivative containing $\sigma^2\lambda^3$ –P=C bond.

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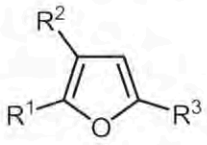
GOLD CATALYSIS AS AN EFFICIENT TOOL FOR THE SYNTHESIS OF HETEROCYCLES

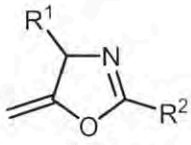
A. Stephen K. Hashmi

Organisch-Chemisches Institut, Ruprechts-Karls-Universität Heidelberg, Im Neuenheimer Feld 270, 69120 Heidelberg, Germany

Gold catalysis has emerged to a powerful tool for organic syntesis.[1] Intramolecular nucleophilic addition reactions of *O*- and *N*-nucleophiles to allenes or alkynes readily delivers different heterocycles like furans 1 and alkylidene oxazolines 2 or 3 with interesting substitution patterns from easily available starting materials.[2,3]



1



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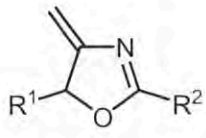
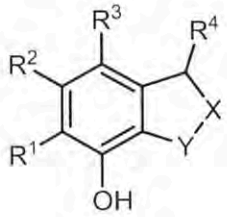


3

Benzoanellated heterocycles 4 and 5 can be obtained by an entirely different reaction which is intiated by the formation of cyclopropyl carbenoids. This methodology allows the synthesis of dihydroindoles, dihydrobenzofurans, dihydroisoindoles, dihydroisobenzofurans, tetrahydroquinolines, chromanes, tetrahydroisoquinolines and isochromanes.[4]



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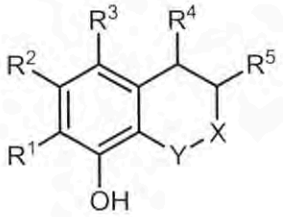
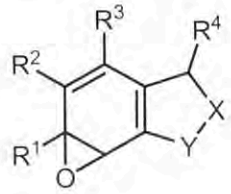


5

X-Y = C-O
O-C
C-N
N-C

This latter route also allows the synthesis of arene oxides 6 or oxepines 7.[5]



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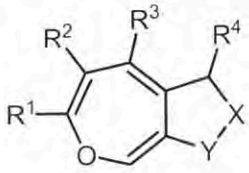


7

In addition to the synthetic aspects the interesting mechanistic aspects will be discussed.

References:

1) Hashmi ASK, Hutchings G, *Angew. Chem.*, 2006; 118, 8064–8105; *Angew. Chem. Int. Ed.*, 2006; 45, 7896–7936.
2) Hashmi ASK, Schwarz L, Choi JH, Frost TM, *Angew. Chem.*, 2000; 112, 2382–2385; *Angew. Chem. Int. Ed.*, 2000; 39, 2285–2288.
3) Hashmi ASK, Weyrauch JP, Frey W, Bats JW, *Org. Lett.*, 2004; 6, 4391–4394.
4) Hashmi ASK, Frost TM, Bats JW, *J. Am. Chem. Soc.*, 2000; 122, 11553–11554.
5) Hashmi ASK, Rudolph M, Weyrauch JP, WölfleM, Frey W, Bats JW, *Angew. Chem.*, 2005; 117, 2858–2861; *Angew. Chem. Int. Ed.*, 2005; 44, 2798–2801

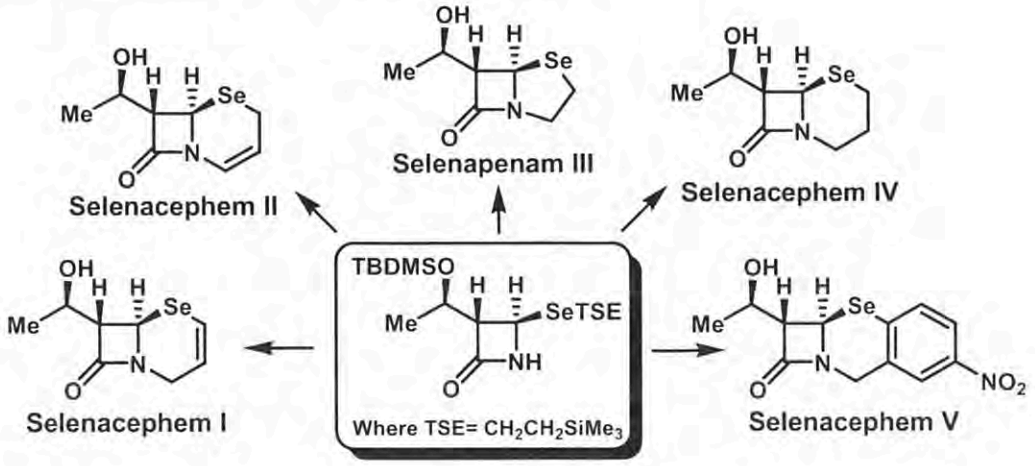
AN EFFICIENT SYNTHESIS OF SELENAPENAMS AND SELENACEPHEMS USING KEY INTERMEDIATE 4-(2-TRIMETHYLSILYLETHYLSELENO)AZETIDINONE

Dinesh R. Garud;[a] Yumiko Kawai;[a] Hiromune Ando;[b] Mamoru Koketsu;[b] Hideharu Ishihara[a]

[a]*Department of Chemistry, Faculty of Engineering,* [b]*Life Science Research Center, Gifu University, Gifu 501-1193, Japan*

The β-lactam (2-azetidinone) skeleton is the key structural element of the most widely employed class of antibacterial agents, the β-lactam antibiotics. The first β-lactam ring system was synthesized by H. Staudinger in 1907,[1] but β-lactams as a class of compounds became attractive only after it was established that penicillin contained a β-lactam unit as the structural feature.[2] Only a few reports can be found on the selenium analogue of β-lactam antibiotics due to difficulties involved in their preparations.[3] Herein, we report our first step towards achieving this goal by demonstrating an elegant method for the synthesis of these compounds.

Selenapenams and selenacephems were synthesized using key intermediate 4-(2-trimethylsilylethylseleno) azetidinone in an extremely simple way. The new selenating reagent was synthesized for this process. Novel intramolecular cycloaddition reaction of selenium with alkyne and allene is used in the present synthesis. The reported chemistry extends the utility of the silyl protection for the synthesis of β-lactams amenable to the preparation of libraries extending beyond the diversity of the analogous accessible from the available source. This method has important advantages over other conceptually similar procedure available because of very high reactivity of the reagent and because of the C-Se bond at stereocenter exerts strong conformational control on β-lactam antibiotics. Stereochemistry and the structure of novel selenacephems (I & IV) and selenapenam (III) were confirmed by X-ray diffraction analysis. The compounds prepared during this study are expected to exhibit interesting biological properties.



References:

[1] Staudinger, H. *Liebigs Ann. Chem.*, 1907; 356, 51-123.

[2] Clarke, HT. Johnson, JR. Robinson, R. *The Chemistry of Penicillin*; Princeton University Press, Princeton, 1949.

[3] a) Alpegiani, M. Bedeschi, A. Perrone, E. Franceschi, G. *Tetrahedron Lett.*, 1986; 27, 3041-3044. b) Carland, MW. Martin, RL. Schiesser, CH. *Tetrahedron Lett.*, 2001; 42, 4737-4739. c) Carland, MW. Schiesser, CH. *Molecules*, 2004; 9, 4664-71. d) Carland, MW. Martin, RL. Schiesser, CH. *Org. Biomol. Chem.*, 2004; 2, 2612-2618. e) Brown, GA. Anderson, KM. Murray, M. Gallagher, T. Hales, NJ. *Tetrahedron*, 2000; 56, 5579-5586. f) Brown, GA. Anderson, KM. Large, JM. Planchenault, D. Urban, D. Hales, NJ. Gallagher, T. *J. Chem. Soc., Perkin Trans. 1*, 2001; 1897-1900.

Tuesday 17th July
Mathews Theatre A
Contibuted Oral Presentations
3:30pm-4:50pm

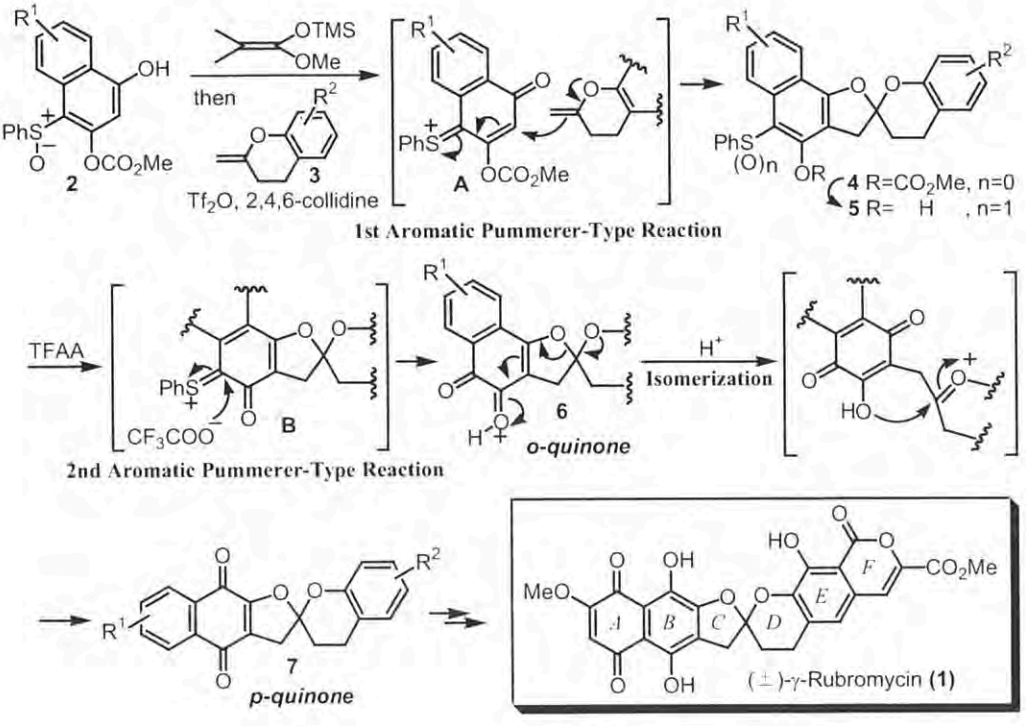
TOTAL SYNTHESIS OF (±)-γ-RUBROMYCIN

Keisuke Kakiguchi,[1] Ikumi Kuriwaki,[1] Shuji Akai,[1, 2] and Yasuyuki Kita[1]

1 Graduate School of Pharmaceutical Sciences, Osaka University,
1-6, Yamada-oka, Suita, Osaka, 565-0871 Japan
2 School of Pharmaceutical Sciences, University of Shizuoka,
52-1, Yada, Suruga-ku, Shizuoka,Shizuoka, 422-8526 Japan

γ-Rubromycin (1) is a potent human telomerase inhibitor (IC_{50}=3μM) isolated from *Streptomyces collinus* and expected to be a lead compound for developing a new type of anticancer drugs. Moreover, 1 has attracted the synthetic interest because of the characteristic bisbenzannelated spiroketal framework. Therefore, much effort has been devoted to the synthesis of 1, but the total synthesis has not yet been reported, because construction of the highly oxygenated ring system was difficult. We present here the first total synthesis of (±)-1.

Our key strategy includes double aromatic Pummerer-type reactions[1)]. Thus, the dibenzospiroketal (4) was obtained by the coupling of the *p*-sulfinylphenol (2) and the 2-methylenechroman (3); regioselective conjugated addition of 3 to the *p*-quinone sulfonium intermediate (A) generated by the first aromatic Pummerer-type reaction and the following spirocyclization. The second aromatic Pummerer-type reaction of the *o*-sulfinylnaphthol (5) produced the *o*-quinone (6). Finally, 6 was successfully isomerized by acid treatment and cyclized to the desired *p*-quinone (7). With these excellent protocols in hand, we achieved the first total synthesis of (±)-1.



Scheme 1

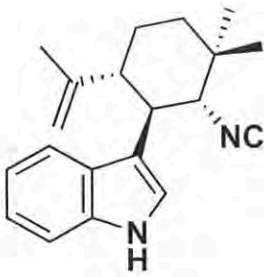
References:
1) Kita Y.; Takeda Y.; Matsugi M.; Iio K.; Gotanda K.; Murata K.; Akai S. *Angew. Chem. Int. Ed. Eng.*, 1997; 36, 1529-1531; Akai S.; Morita N.; Iio K.; Nakamura Y.; Kita Y. *Org. Lett.*, 2000; 2, 2279-2280; Review, "*Recent Advances in Pummerer Reactions*", Akai S.; Kita Y. *Top. Curr. Chem.*, 2007; 274, 35-76.

NEW PROCESSES FOR THE SYNTHESIS OF BIOLOGICALLY RELEVANT HETEROCYCLES

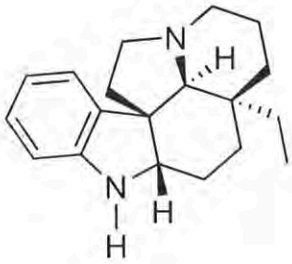
Martin G Banwell

Research School of Chemistry, The Australian National University, Canberra, ACT 0200

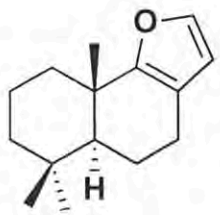
The biologically active natural and non-natural products shown below have been or are currently the subject of synthetic studies in our laboratories. A common thread in all of these studies has been the desire to develop new methodology for preparing the associated heterocyclic ring systems. This lecture will attempt to highlight the benefits of using such methodologies.



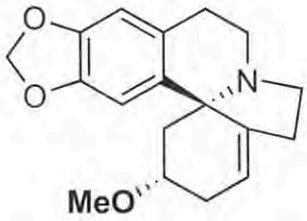
Hapalindole C



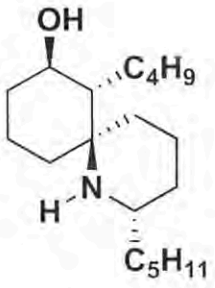
(±)-Aspidospermidine



(±)-Pallescensin A



(-)-Erythramine



Perhydrohistrionicotoxin

References:

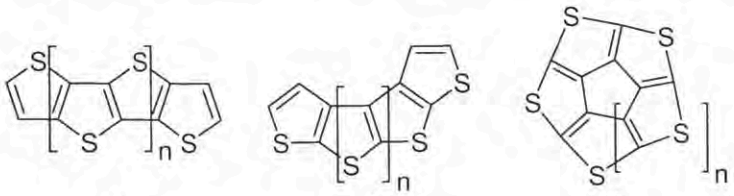
Banwell MG, Beck DAS, Stanislawski PC, Sydnes MO and Taylor RM, *Current Organic Chemistry*, 2005, 9, 1589.

NEW ADVANCES IN SYNTHESIS OF POLYANNULATED THIOPHENES

K. Yu. Chernicheko, V. V. Sumerin, S. S. Vshyvenko, E. S. Balenkova, V. G. Nenajdenko

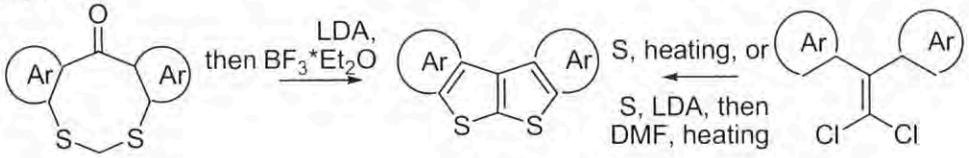
Department of Chemistry, Moscow State University, Moscow, Russia

Recently our group focused on the synthesis of structures, containing polyannulated thiophenic fragments – potential candidates for material science.
Different types of thiophenic rings junction lead to linear oligothiophene 1 or helical 2. Frameworks 1 and 2 reach the empirical formula C_2S when $n\rightarrow\infty$, that is, in the case of a polymer, thus giving rise to a new form of carbon sulfide. A helical structure could be closed to give a macrocycle, thus forming the circulene 3, which consists of thiophenic rings with an empirical formula $(C_2S)_n$ for any number of rings.

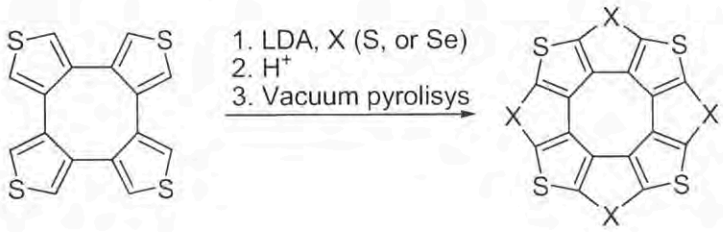


1 2 3

We have developed short and straightforward method for the synthesis of the annulated polythiophenes containing dithienothiophene moiety by cyclization of corresponding dithiaoctanones with strong base. After synthesis of two initial (Ar=2,3-*b* thienyl or 3,2-*b* thienyl) examples [1] we have found that this method have a common nature and the origin of Ar can be broadly varied (benzothienyl, etc).



Another short-cut towards these structures involves easy available 1,1-dichloro-2,2-diarylalkenes as precursors. When Ar=3-benzothienyl, corresponding polythiophene can be obtained by heating with elemental sulphur in high-boiling (>200 °C) inert solvent or by treating with LDA/sulphur followed by heating in DMF. Depending on the nature of Ar one of this method or both can be used to accomplish transformation.
Very recently we have reported effective synthesis of the first fully heterocyclic circulene – Sulflower [2] (X=S).



Sulflower was thoroughly characterized, including X-ray diffraction. We have also synthesized mixed sulphur-selenium circulene (X=Se) and now are underway towards Sulflower analogs, containing another heteroatoms and another macrocycle sizes.

References:
1. Nenajdenko VG, Sumerin VV, Chernichenko K Yu, Balenkova ES. *Org. Lett.*, 2004, 6, 3437-3439.
2. Chernichenko K Yu, Sumerin VV, Shpanchenko RV, Balenkova ES, Nenajdenko VG. *Angew. Chem. Int. Ed.*, 2006, 45, 7367-7370.

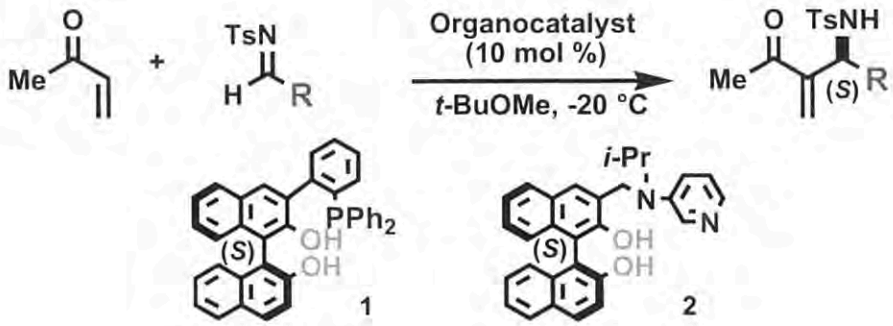
BIFUNCTIONAL CHIRAL ORGANOCATALYSTS FOR THE ENANTIOSELECTIVE AZA-MORITA-BAYLIS-HILLMAN REACTION

Katsuya Matsui, Atsushi Horii, Koichi Tanaka, Shinobu Takizawa and Hiroaki Sasai

The Institute of Scientific and Industrial Research (ISIR), Osaka University,

8-1 Mihogaoka, Ibaraki-shi, Osaka 567-0047, Japan

Two types of bifunctional organocatalysts which bear Lewis base unit and Brϕnsted acid unit in the single catalyst molecule have been developed. The organocatalysts show high catalytic activity and enantioselectivity towards various kinds of aldimines as shown below. Enantioselectivity obtained by catalyst 2 is shown in parenthesis. In the case of the diphenylphosphinophenyl substituted organocatalyst 1, axial chirality between the naphthyl ring and the phenyl ring seems to have a crucial role to achieve high catalytic activity and enantioselectivity. For the pyridylaminomethyl substituted organocatalyst 2, hydrogen-bonding between the amino group and the phenolic hydroxy group is important to fix the conformation of the organocatalyst.



Entry	R	Time (h)	Yield (%)	Ee (%)	
1	*p*-Cl-C6H4 -	144	90	92	(95)[a]
2	*p*-Br-C6H4 -	96	87	92	(94)[a]
3	*p*-OMe-C6H4 -	216	90	95	(94)[a]
4	*p*-Et-C6H4 -	192	Quant	93	(93)[a]
5	*o*-Cl-C6H4 -	144	96	92	(62)[a]
6	1-Naphthyl	360	85	90	(70)[a]
7	2-Furyl	72	93	94	(88)[a]

a (*R*)-product was formed

References:

1) Matsui K. Takizawa S. Sasai H. *J. Am. Chem. Soc.* 2005, 127, 3680-3681.

2) Matsui K. Tanaka K. Horii A. Takizawa S. Sasai H. *Tetrahedron: Asymmetry*, 2006, 17, 578-583.

3) Matsui K. Takizawa S. Sasai H. *Synlett*, 2006, 761-765.

Tuesday 17th July
Mathews Theatre B
Contibuted Oral Presentations
3:30pm-4:50pm

SYNTHESIS AND FLUORESCENCE CHARACTERISTICS OF 2-N-METHYLANILINOPYRIDINE AND 2-N-ETHYLANILINOPYRIDINE: EFFECT OF TRANSITION METAL

Zaharah Aiyub, Zanariah Abdullah and Mohd Fairuz Zainal Abidin

Chemical Synthesis and Modelling Research Group

Department of Chemistry, Fac. of Science, University of Malaya, 50603, Kuala Lumpur

Email: zaharaa@um.edu.my

Tel. No: 0379674081

The fluorescence characteristic of pyridines are not extensively studied, eventhough a wide variety of heterocyclic compounds are known to be fluorescent. There is not much understanding between fluorescence-solvents relationship and metal-fluorescence characteristics. However, results from previous studies have shown that the fluorescent characteristics of heterocyclic compounds are dependent on the solvents used and its complexes are found to be dependent on the different metals used[1]. 2-*N*-methylanilinopyridine and 2-*N*-ethylanilinopyridine were obtained when 2-chloropyridine was refluxed with *N*-methylaniline and *N*-ethylaniline respectively. The structures of both compounds were confirmed by spectroscopic methods. The two ligands were reacted with acetate salts of manganese(II) and zinc(II), copper(II)nitrate and nickel(II) carbonate in ethanol in a 1:2 ratio (metal: ligand). Fluorescence studies were conducted using methanol as the solvent, with the same concentration. Both 2-*N*-methylanilinopyridine and 2-*N*-ethylanilinopyridine showed similar fluorescence peak at 341 nm and 675 nm, and 341 nm and 677 nm respectively when excited at 311 nm. Mn(II) and Zn(II) complexes of 2-N-methylanilinopyridine gave lower fluorescence peak compared to its ligand. Mn(II) complex showed peaks at 281 nm and 567 nm when excited at 285 nm and the Zn(II) complex gave peaks at 307 nm and 504 nm when excited at 252 nm. Cu(II) and Ni(II) complexes however showed an increase in the first peak and a decrease in the second peak compared to its ligand. Fluorescence was observed at 350 nm and 495 nm when excited at 248 nm for the Cu(II) complex and 359 nm and 523 nm when excited at 262 nm for the Ni(II) complex. Mn(II), Cu(II) and Zn(II) complexes of 2-*N*-ethylanilinopyridine gave lower fluorescence peaks compared to its ligand. Mn(II) complex showed peaks at 281 nm and 569 nm when excited at 286 nm, Cu(II) complex showed peaks at 302 nm and 599 nm when excited at 283 nm while the Zn(II) complex showed peaks at 307 nm and 608 nm when excited at 255 nm. Ni(II) complex however showed an increase in the first peak and a decrease in the second peak compared to 2-*N*-ethylanilinopyridine. Fluorescence of Ni(II) complex was observed at 397 nm and 485 nm when excited at 400 nm. The fluorescence intensity for metal complexes of 2-*N*-methylanilinopyridine and 2-*N*-ethylanilinopyridine is lower compared to 2-*N*-methylanilinopyridine and 2-*N*-ethylanilinopyridine.

References:

1. Abdullah Z., Mohd Tahir N., Abas M.R., Aiyub Z., Low B.K., *'Fluorescence studies and selected 2-alkylaminopymirimidines'*, *Molecules*, 9, 2004, 520-526.
2. Rurack K., Resch U., Senoner M., and Dahne S., *' A new fluorescence probe for trace metal ions: Cation-dependent spectroscopic properties'*, *J. of Fluorescence*, 3, No. 3, 1993, 141-143.

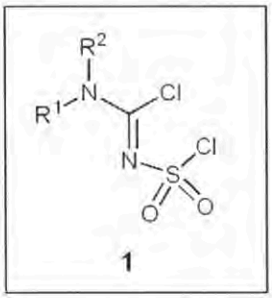
N,N-DIALKYL-N'-CHLOROSULFONYL CHLOROFORMAMIDINES IN THE SYNTHESIS OF NOVEL HETEROCYCLES

Cablewski, T[1]; Carter, EJ[2]; Francis, CL[1*]; Jahangiri, S[1]; Liepa, AJ[1]; Perkins, MV[2]; Woodgate, RCJ[1]

[1] *CSIRO Molecular & Health Technologies, Clayton VIC, Australia*

[2] *School of Chemistry, Physics and Earth Sciences, Flinders University, Bedford Park SA, Australia*

N,N-Dialkyl-*N'*-chlorosulfonylchloroformamidines 1 were found to be versatile 1,3-dielectrophilic intermediates for the synthesis of a cornucopia of new and uncommon heterocycles. Reactions of 1 with 1,2-, or 1,3-dinucleophiles led to 5- and 6-membered heterocyclic products, respectively. Thus, reaction of 1 with hydrazines or hydroxamic acids gave [1,2,3,5]thiatriazoles 2 and [1,3,2,4]oxathiadiazoles 3.[1] Treatment of 1 with several 2-amino-1-azaheterocycles afforded fused [1,2,4,6]thiatriazines 4 and/or 5.[2,3,4] The reaction of 1 with 2-mercapto-1*H*-azaheterocycles or cyclic 1,3-dicarbonyl compounds provided fused [1,4,2,6]dithiadiazines 6[4] and fused [1,4,3]oxathiazines 7[5]. This paper reports on the synthesis, regioselectivity during formation, and some reactions of such products.



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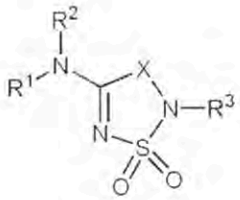
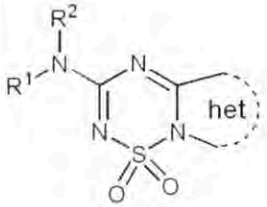


2 X=NR[4]
3 X=O



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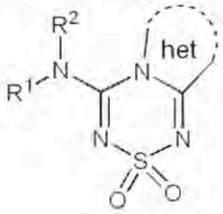

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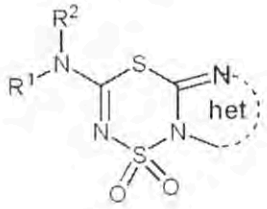

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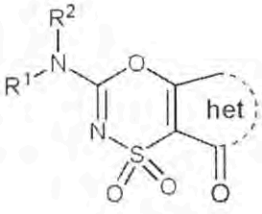

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References:

1. Fallon GD, Jahangiri S, Liepa AJ & Woodgate RCJ, *Aust. J. Chem.*, 2005; *58*, 332.

2. Fallon GD, Francis CL, Johansson K, Liepa AJ & Woodgate RCJ, *Aust. J. Chem.*, 2005; *58*, 891.

3. Cablewski T, Carter EJ, Francis CL, Liepa AJ & Perkins MV, *Aust. J. Chem.*, 2007; *60*, 105.

4. Cablewski T, Francis CL & Liepa AJ, unpublished results.

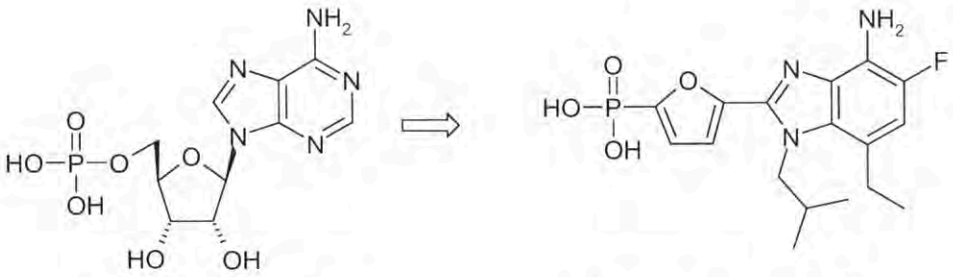
5. Cablewski T, Francis CL & Liepa AJ, *Aust. J. Chem.*, 2007; *60*, 113.

DISCOVERY OF NOVEL BENZIMIDAZOLE PHOSPHONATES AS NON-NUCLEOTIDE AMP-MIMETICS TO INHIBIT FBPASE WITH IN VIVO EFFICACY IN RATS

Qun Dang, Mark D. Erion, Srinivas Rao Kasibhatla, K. Raja Reddy, M. Rami Reddy, and Paul D. van Poelje

Metabasis Therapeutics, Inc., 11119 North Torrey Pines Road, La Jolla, CA 92037, USA

Fructose-1,6-bisphosphatase (FBPase) is a rate-limiting enzyme of gluconeogenesis (GNG), and increased flux through the GNG pathway has been implicated as the main cause for the abnormally high hepatic glucose output in type 2 diabetes (T2DM). Consequently, inhibition of FBPase has potential as a new approach to treatment of T2DM. Using a structure-based drug design approach targeting the allosteric AMP-binding site, we discovered a series of benzimidazole phosphonate FBPase inhibitors.[1,2] The lead compound, GP04383, inhibited human FBPase with high potency (IC_{50} = 55 nM) and specificity. GP04383 also inhibited GNG in primary hepatocytes and lowered glucose following i.v. administration to normal fasted rats. The design, synthesis and SAR of a series of benzimidazole FBPase inhibitors will be presented.



AMP, IC_{50} = 1000 nM **GP04383, IC_{50} = 55 nM**

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APPLICATION OF AZOMETHINE YLIDE CHEMISTRY TO THE PREPARATION OF SEVEN-MEMBERED RING HETEROCYCLES: 1,3-BENZODIAZEPIN-5-ONES

Jose A. Basutto,[A] Pawel G. Jokisz,[A] Adam G. Meyer,[A] John H. Ryan,[A] Nadia Spiccia,[A] Jonathan M. White[B] and Leon S.-M. Wong[A]

[A] *CSIRO Molecular and Health Technologies, Bag 10, Clayton South Victoria 3169, Australia*

[B] *Bio21 Institute of Molecular Science and Biotechnology, The University of Melbourne, Parkville Victoria 3010, Australia*

Azomethine ylides undergo a wide variety of [3+2] cycloaddition reactions to give five-membered ring products.[1] We initiated a program of study of azomethine ylide chemistry by exploring scope and limitations of the reaction of a non-stabilised azomethine ylide with arylcarboxaldehydes.[2,3] We now report that exposure of isatoic anhydrides 1 with *N*-methoxymethyl-*N*-(trimethylsilylmethyl)benzylamine (2)[4] in the presence of catalytic TFA, results in isolation of novel 1,3-benzodiazepin-5-ones 3. We present an investigation of the scope of this reaction using a range of substituted isatoic anhydrides 1 (R = H, alkyl, phenyl). Furthermore, we have found evidence that the reaction proceeds via 1,3-dipolar cycloaddition of the ylide 4, generated *in situ* from precursor 2, to the most activated carbonyl group of 1, to afford a spiro-fused isoxazolidine 5, which then undergoes loss of carbon dioxide to form the seven-membered ring product 3.

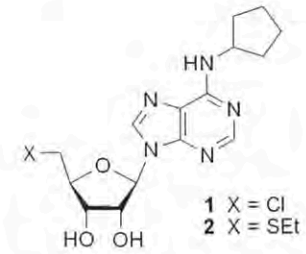
Tuesday 17th July
Mathews Theatre C
Contibuted Oral Presentations
3:30pm-4:50pm

IMPROVED SYNTHETIC APPROACHES TOWARD 5'- AND N^6-FUNCTIONALISED ADENOSINE DERIVATIVES

Trent D. Ashton, Shane Devine, Peter J. Scammells

Department of Medicinal Chemistry, Victorian College of Pharmacy, Monash University, 381 Royal Parade, Parkville VIC 3052

Adenosine analogs which are substituted at N^6 and/or modified at the 5'-position have been the subject of widespread interest. Many N^6-substituted 5'-modified adenosines act as adenosine agonists and partial agonists (e.g. compounds **1**-**3**) and the nature of the groups in the N^6 and 5'-positions exhibit a profound influence on receptor affinity and subtype selectivity. Compounds of this type have also been used as agents for positron emission topography imaging of brain A_1 adenosine receptors. Furthermore, 5'-modified adenosines have featured prominently in studies on the biological methylating agent, methyl transferase *S*-adenosyl-L-methionine. The 5'-aziridine based SAM mimic **4** is one such example. Antibiotics that inhibit *Mycobacterium tuberculosis* have also been identified that possess a heteroatom motif in the 5'-position (e.g. compound **5**).



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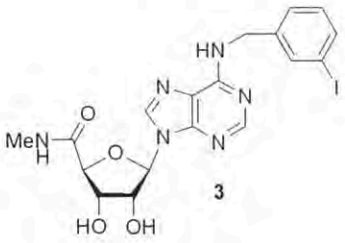
2 X = SEt



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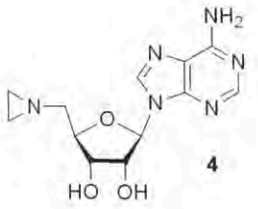

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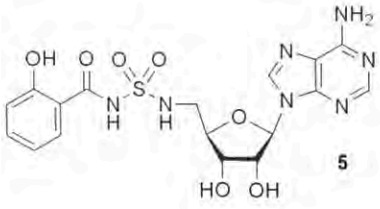

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We have recently developed two short and efficient syntheses of N^6-substituted 5'-modified adenosines. The first approach employs inosine as the starting material and the 5'- and 6-positions are simultaneously activated for subsequent substitution in the key step.[1,2] In the second approach, the 5'-position of tetraacetyl ribose is selectively deprotected utilising a lipase enzyme and, after subsequent modification, the ribose unit is attached to the desire purine *via* a microwave mediated coupling.[3]

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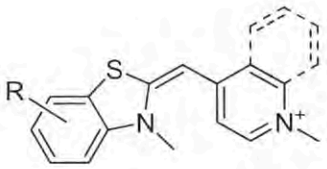
SYNTHESES AND DNA –BINDING STUDIES OF CYANINE DYES.

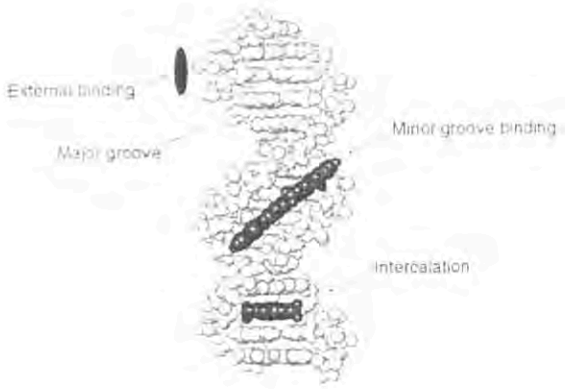
Gunnar Westman, Merima Hasani and Chadi Saliba

Department of Chemical and biological Engineering, Chalmers University of Technology,

412 96 Goteborg, Sweden

Compounds that bind to DNA have received considerable attention due to their potential as anti-tumor drugs. Cyanine dyes exhibit a dramatic enhancement in fluorescence intensity upon binding to DNA. We have developed a series of unsymmetrial cyanine dyes that bind in the minor groove of DNA instead of by intercalation. Their binding in the minor groove is not expected to significantly lengthen the DNA-helix. In this presentation the synthesis and binding properties of the compounds will be presented.





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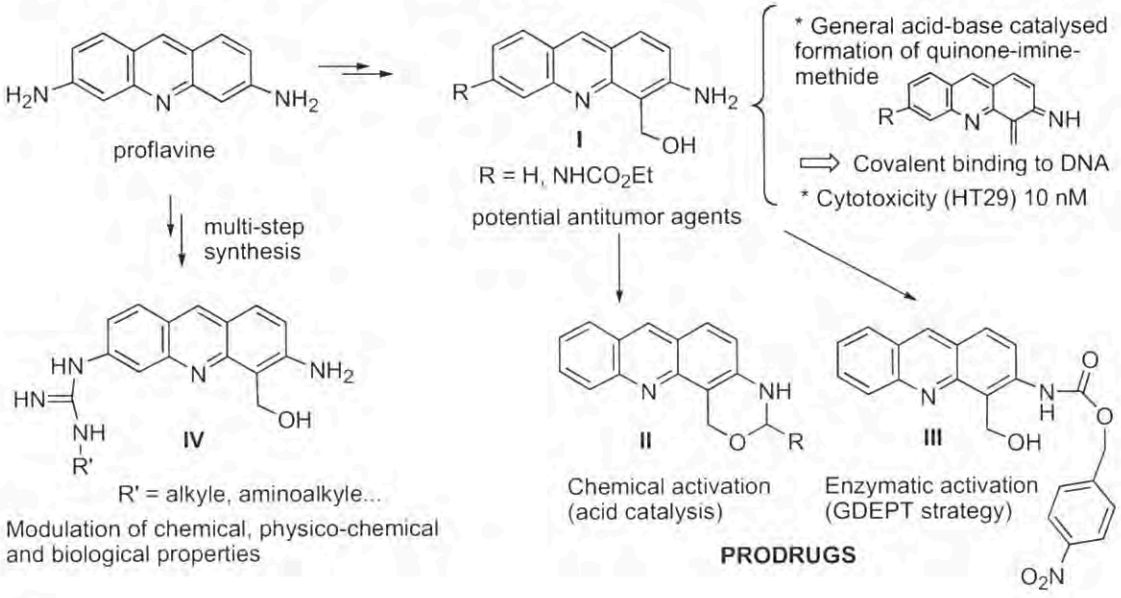
SYNTHESIS OF GUANIDINO SUBSTITUTED ACRIDINES, PRECURSORS OF CYTOTOXIC QUINONE-IMINE-METHIDE INTERMEDIATES

Walid Zeghida, Myriam Ouberaï, Pascal Dumy and Martine Demeunynck

Department of Molecular Chemistry, UMR CNRS 5250, Université Joseph Fourier, BP53, 38041 Grenoble, France

We have previously designed a series of acridine derivatives such as I, that display significant cytotoxicity against various cancer cell lines.[1] QSAR data showed that the presence of ortho-(hydroxymethyl) amino functionality is determinant for the antitumor properties. These molecules interact with DNA by intercalation and covalently bind to the macromolecule through formation of a highly electrophilic quinone-imine-methide (QIM) intermediate. In an effort to modulate the biological properties and decrease the in vivo toxicity, we have prepared two series of prodrugs, which may be activated either chemically (II)[2] or enzymatically (III).[3]

Another strategy consists in modulating the properties by modifying the left part of the molecules keeping untouched the reactive part. We have chosen to transform one amino group of proflavine into one N,N'-disubstituted guanidine (such as IV), via intermediate formation of carbamoylated thiourea. The multi-step synthesis includes as key-steps several protection/deprotection reactions and one regioselective electrophilic aromatic substitution (in 11N HCl) followed by intramolecular transcarbamoylation in methane sulfonic acid generating the oxazinone ring precursor of the active ortho-hydroxymethyl amine. Isolation and purification of these highly functionalised molecules are challenging, and in particular the high polarity and reactivity of the final molecules IV severely limit the use of most purification procedures. The new molecules display sub-micromolar cytotoxicity. Other properties such as cell distribution and DNA binding are under investigations.



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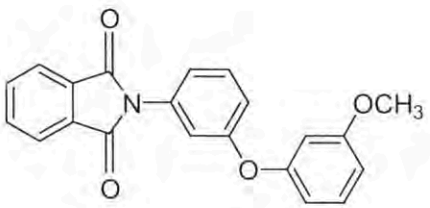
PHARMACOPHORE - BASED DESIGN AND SYNTHESIS OF A NEW INHIBITOR OF THE NORA BACTERIAL EFFLUX PUMP

Tom Dupree[a], Jody Morgan[a], Burak Coban[b] and John B. Bremner[a]*

[a] *Department of Chemistry, University of Wollongong, NSW 2522, Australia*

[b] Department of Chemistry, Zonguldak Karaelmas University, Zonguldak 67100,Turkey.

Bacterial efflux pumps are one of the major mediators of multidrug resistance (MDR) to antibacterial agents.[1] One way to combat resistance is to combine traditional antibacterials with agents that inhibit the efflux pump activity. In the pathogenic bacterium *Staphylococcus aureus*, the NorA pump is one of the efflux pumps which compromises the potency of a number of antibacterials including the fluoroquinolones and the alkaloid berberine.[2] In order to provide a basis for the future development of potent and selective inhibitors of the NorA efflux pump, a ligand-based drug design program has been initiated. Using the programme Catalyst®, the first pharmacophore has been developed for small molecule inhibitors of the NorA bacterial multidrug resistance pump in *Staphylococcus aureus*. The predictive capability of the pharmacophore was demonstrated with the *de novo* design and synthesis of a new inhibitor (1). This pharmacophore has the potential to inform new inhibitor design and structure-activity relationships. The pharmacophore generation, as well as design and synthetic aspects, will be discussed.



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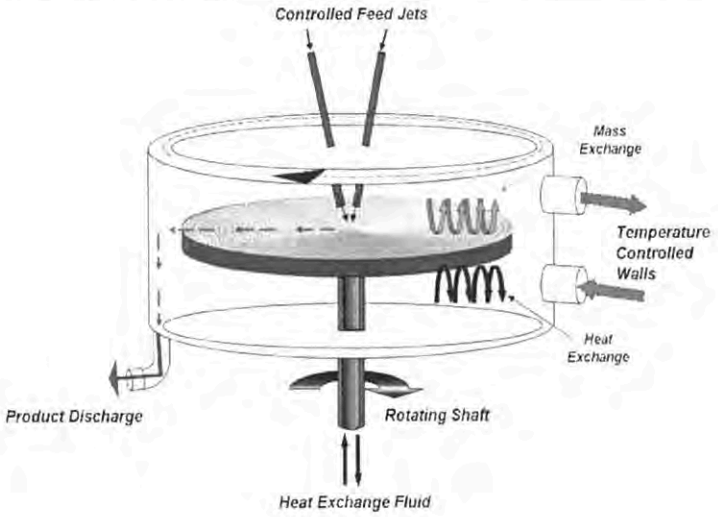
Tuesday 17th July
Mathews Theatre D
Contibuted Oral Presentations
3:30pm-4:50pm

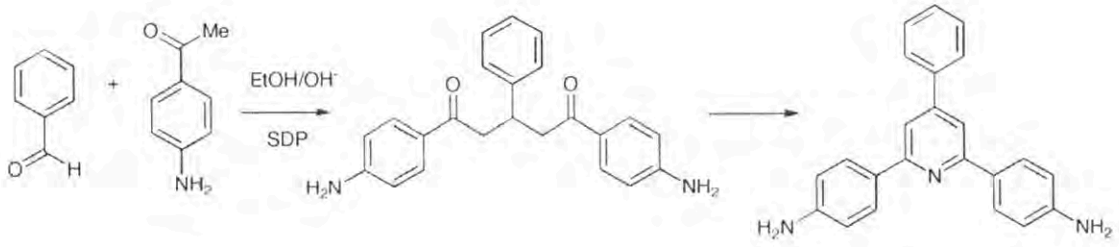
ROTATING SURFACES IN FACILITATING CHEMICAL TRANSFORMATIONS

Smith, Nicole[1]; Norrett [1], Marck; Raston, Colin[1]

[1]*Centre for Strategic Nano-Fabrication, School of Biomedical, Biomolecular and Chemical Sciences, University of Western Australia, Crawley, WA 6009, Australia.*

Organic synthesis has traditionally been carried out using batch technology both in the laboratory and in production. There is a need to improve the green chemistry metrics of chemical reactions, and much has been done in using alternative reaction media, the use of solventless reactions, and indeed the use of alternative energy sources to control the outcome of reactions. The latter includes the use of microwave energy. Our approach is to use developments in process intensification (PI) to improve the green chemistry metrics of chemical reactions. PI attempts to treat all molecules in a reaction in the same way. One technology under the umbrella of PI is spinning disc processing (SDP), a cartoon of an SDP reactor is shown below.[1,2] With SDP reagents are fed on to the disc, close to its centre, and under shear forces associated with the disc rapidly rotating the reagents are rapidly mixed thereby creating very fast kinetics. There are several control parameters for SDP including speed, rate of flow, concentration, temperature, and surface roughening effect. The limitation SDP is the short resident time of the fluid on the disc, typically less than a second. Nevertheless this is sufficient for some reactions. For example, the 1,5-diketone in the scheme is formed in high yield in ethanol in the presence of base on a single pass on the SDP. This can be readily converted to the Krohnke pyridine on treatment with ammonium acetate in PEG.[3]





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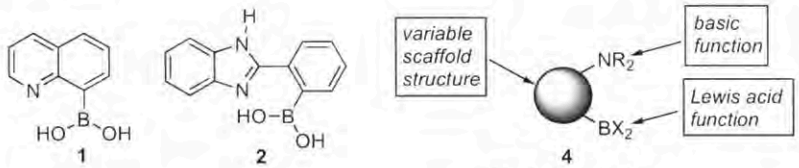
SYNTHESIS AND GREEN APPLICATIONS OF ORGANIC, BIFUNCTIONAL CATALYSTS BORONIC ACID FUNCTIONALIZED NITROGEN HETEROCYCLES.

Karel Aelvoet, Kenny Arnold, Christophe Grosjean, Damine Herault, Thorben Schütz, Andy Whiting.*

Chemistry Department, Durham University, Science labs, South Road, Durham DH1 3LE, UK.

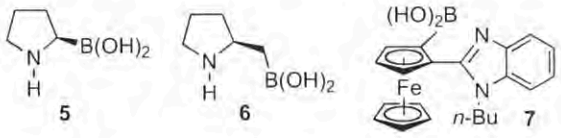
Around the early '60s, Letsinger showed[1] that amino-boronic acid systems 1 and 2 are capable of cooperative catalytic effects, through both the aromatic nitrogen and boronic acid functions. With a background in the applications of boronates in synthesis and for catalytic applications,[2] we have become involved in a project which involves the synthesis[3] and application[4] of a range of bifunctional amino-boronic acid catalysts.



1 2 4

Model catalyst

In this presentation, we discuss the asymmetric synthesis of novel catalytic amino-boronate systems, such as 5 to 7, using both asymmetric directed metallation and chiral auxiliary-based approaches. The solid-state and solution structures of these types of systems has also been examined, particularly as a function of pH, and we have used these types of compounds for a range of useful synthetic reactions, particularly in water or under water tolerant conditions. These reactions include the aldol, Mannich, Michael addition, Baylis-Hillman, Biginelli and others, where moderate to good catalytic has been observed and mechanistic studies have been undertaken to examine the mode of action of these types of catalysts.



5 6 7

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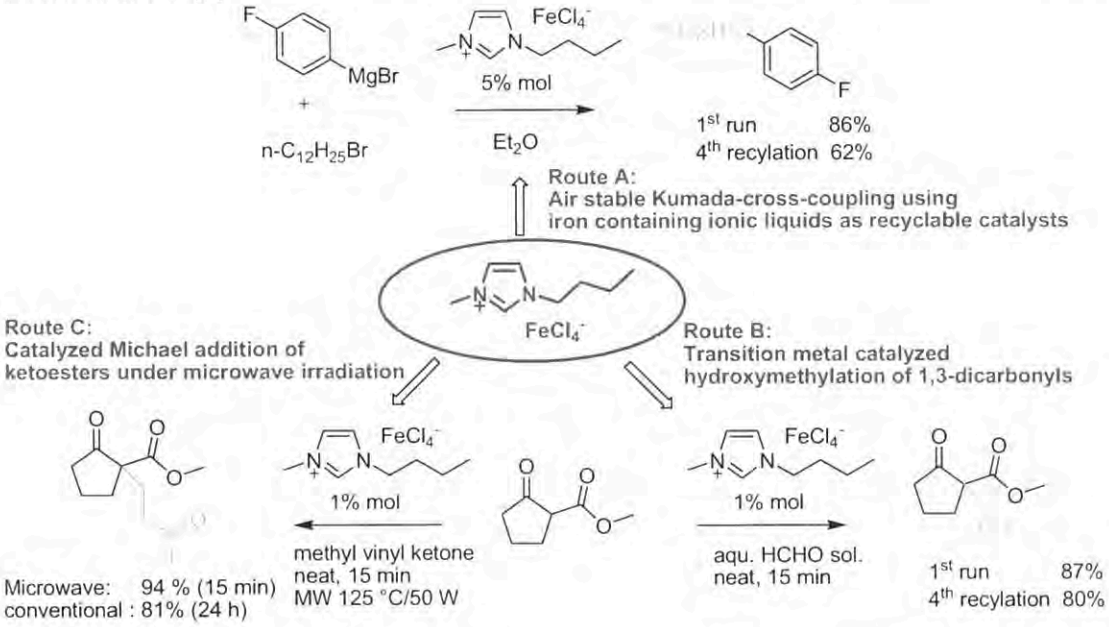
METAL CONTAINING IMIDAZOLIUM IONIC LIQUIDS AS EFFICIENT AND RECYCLABLE CATALYSTS IN C-C-BOND FORMATION

Peter Gaertner, Katharina Bica, Thiti Junpirom

Vienna University of Technology, Vienna, Austria

In the last decades, ionic liquids (ILs) have attracted considerable attention as alternatives to environmentally damaging organic solvents and as new reaction media for chemical reactions and separation techniques [1]. The aim of our work is to extend the application of ILs beyond their use as mere reaction media and develop ILs serving as catalyst itself. Since iron is known as one of the most inexpensive and non-pollutant metals we are especially interested in the application of iron containing IL catalysts [2].
In the course of our investigations we discovered that the iron containing IL butylmethylimidazolium tetrachloroferrate (bmim-$FeCl_4$) is a very efficient and recyclable catalyst for various C-C-bond formation reactions [3].



We could establish the ionic liquid butylmethylimidazolium tetrachloroferrate (bmim-$FeCl_4$) as very effective and completely air stable catalyst for the biphasic Grignard cross coupling with primary and secondary alkyl halides bearing β-hydrogens. After simply decanting the product in the ethereal layer, the ionic liquid catalyst was successfully recycled 4 times.
Further investigations dealing with iron catalyzed Michael addition proved that bmim-$FeCl_4$ also is a very efficient catalyst for microwave assisted synthesis, giving a strong acceleration of the reaction rate compared to thermal heating (Route B).
Hydroxymethylation of various 1,3-dicarbonyls also proceeded extremely satisfying since a very low catalyst loading - up to 0.1% - could be achieved. Various other metal containing imidazolium salts (Cu(II), Ti(IV), Co(II) and Ni(II)) were examined, but the cheap and environmentally benign iron salt proved to be superior (Route C).
Currently the preparation and application of chiral metal containing ILs as recyclable chiral catalysts for transition metal catalyzed asymmetric synthesis is investigated.

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ENVIRONMENTAL BENIGN SYNTHESIS OF SOME NOVEL BIODYNAMIC HETEROCYCLES AND THEIR BIOLOGICAL ACTIVITY

D Ashok* , D Shravani and K Sudershan[a]

Department of Chemistry, P G College of Science, Saifabad, Masab Tank,

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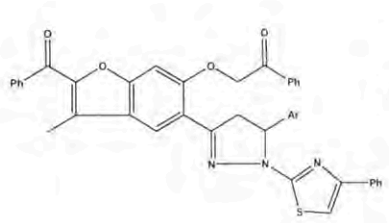
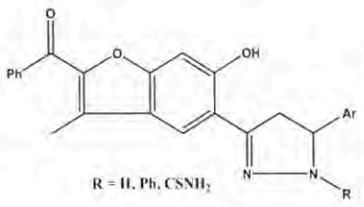
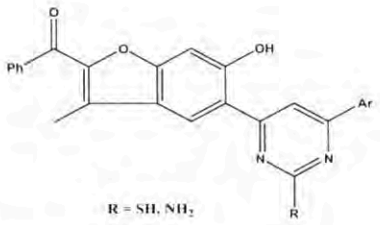
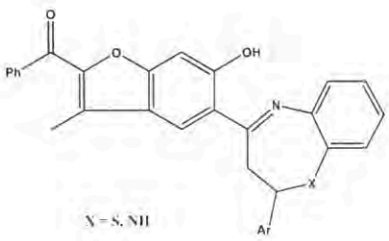
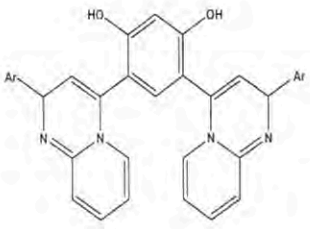
Heterocyclic compounds display a wide variety of biological properties, many of which can be exploited for medicinal purposes and are also essential for the human life. Therefore methods for the synthesis of such systems are of significant interest. The environmental protection has become a global concern and the synthetic organic chemists are searching the ways of developing and applying more efficiently and environmentally benign strategies for future sustainable growth. One of the thrust areas for achieving this target is the environmentally friendly, solvent free approach that involves the exposure of neat reactants to microwave irradiation to give high yield of pure products. The salient features of this high yield protocol are, enhanced reaction rate, easy workup, enhanced yields, operational simplicity, greater selectivity and experimental ease of manipulation, low cost and economical. In view of the environmental benign role of solvent free approach under microwave irradiation, the biopotential of heterocyclic compounds and as a part of our ongoing research programme towards the *Green synthesis*, the concept of *Microwave assisted Organic Reaction Enhancement (MORE) Chemistry* has been adopted for the rapid and efficient synthesis of some novel biodynamic heterocycles of biological interest. All the new heterocyclic compounds synthesized in the present investigation were characterized by their analytical and spectral data such as IR, UV, ^{1}H-NMR, ^{13}C-NMR & Mass, and screened for their antibacterial and antifeedant activities.

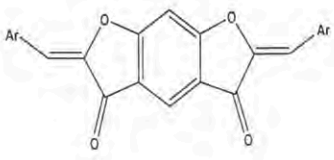












Tuesday 17th July
Poster Abstracts

Tuesday 17th July
Poster Abstracts

TP01

SYNTHESIZE WITH HIGH PURITY OF 5-CHLORO-2, 3-DIFLUORO PYRIDINE AS AN INTERMEDIATE FOR AGROCHEMICALS AND PHARMACEUTICAL

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abbas_ahmady_3957@yahoo.com
[2] Industrial Pesticides Research Centre, Karaj, Iran.

Difluoropyridines generally have high thermal stability and are useful agricultural chemicals particularly as pre-emergence herbicides where they are effective in controlling a variety of noxious weeds. For instance, 5-Chloro-2, 3-difluoro pyridine, can be used for the preparation of pyridinyloxphenoxy alkanecarboxilic acid derivatives, which are herbicides with particularly advantageous properties. This compound was synthesized with higher yield in comparison with previous methods, by using new technique and blended catalysts in two blended polar aprotic solvents. After synthesizing, the product was separated from the reaction mixture by slow fractional distillation with heat-sealed vigorous column.

This compound is an important starting material for the preparation of Agrochemicals and Pharmaceutical compounds.

Key words: Difluoropyridines, Herbicides, Pharmaceuticals, pyridinyloxphenoxy alkanecarboxilic acid, Blended catalysts.

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[3] Venugopal J, Balakrishnan C, Rouge B, European Patent, 1995, 710, 649.

TP02

SYNTHESIS OF 3,3,4-TRIARYL-3,4-DIHYDROBENZO[*f*]QUINOLINES; A NEW CLASS OF T-TYPE PHOTOCHROMIC SYSTEM

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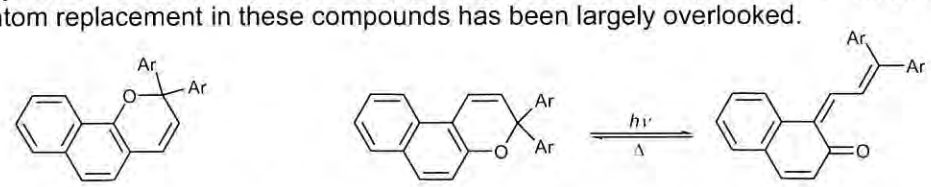
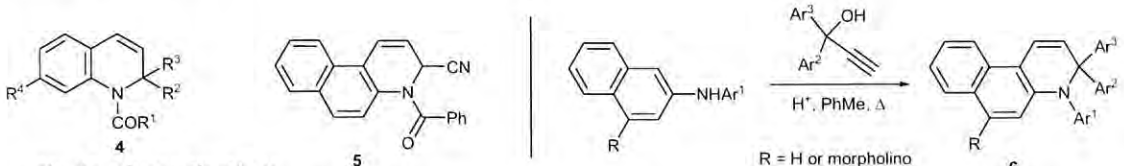
Derivatives of the naphtho[1,2-*b*]pyans 1 and naphtho[2,1-*b*]pyrans 2 undergo photoinduced electrocyclic ring opening to a coloured merocyanine valence tautomer *e.g.* 3, which thermally reverts to 2 when irradiation ceases (T-type behaviour). Compounds 1 and 2 represent the most commercially significant classes of photochromic compound, and many derivatives of these systems have been synthesised [1]. Despite all this activity it is rather surprising that heteroatom replacement in these compounds has been largely overlooked.



1 2 3

Earlier it had been observed that Reissert compounds such as 4a and 5 were photochromic at -196 °C [2]. Acid-containing polymer films of 4b colour irreversibly [3]. The similarity of the latter and 5 with 2 is apparent. We have investigated the acid-catalysed condensation between readily available 2-(arylamino)naphthalenes and 1,1-diarylprop-2-yn-1-ols and found that this reaction provides 3,3,4-triarylbenzo[*f*]quinolines 6 which exhibit T-type photochromism at ambient temperature in solution. The influence of substituents in the aryl groups and in the naphthalene ring upon the photochromic properties of these compounds will be described.



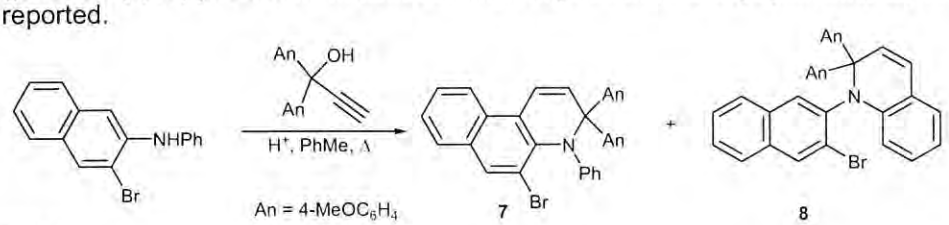
4 5 6

a R^1 = OEt, R^2 = CN, R^3 = R^4 = H
b R^1 = Ph, R^2 = Ph, R^3 = 4-$Et_2NC_6H_4$, R^4 = NMe_2

R = H or morpholino

Cyclocondensation of 3-bromo-2-(phenylamino)naphthalene with 1,1-dianisylprop-2-yn-1-ol proceeded anomalously to give a mixture of 7 and 8. Aspects of this chemistry will be discussed.

In addition, a new approach of potential for the synthesis of 2 and 6 involving Pd-mediated couplings of diarylpropynols with functionalised 2-naphthols and 2-(arylamino)naphthalenes will be reported.



An = 4-$MeOC_6H_4$ 7 8

References:

[1] Van Gemert B, in *Organic Photochromic and Thermochromic Systems, Volume 1: Main Photochromic Families*, eds. Crano JC, Guglielmetti RJ, Plenum Press, New York, 1999, pp. 111-140; Heron BM, Hepworth, JD, *Functional Dyes*, ed. Kim, S-H, Elsevier, Amsterdam, 2006, pp. 85-135.

[2] Kolc J, Becker RS, *J. Am. Chem. Soc.* 1969, 91, 6513-6514; Brettle J, Trundle C, *US Patent*, 4 812 171 (1989).

[3] Berneth H, *US Patent*, 5 391 748 (1995).

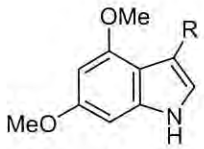
TP03

SYNTHESIS AND REACTIVITY OF SOME DIMETHOXY ACTIVATED INDOLES, BENZIMIDAZOLES AND BENZOTHIAZOLES

Mahiuddin Alamgir*, David St. C. Black, Naresh Kumar

School of Chemistry, The University of New South Wales, NSW-2052, Australia

Strategically positioned methoxy substituents at C4 and C6 in indoles have shown some characteristic reactions at C7, which do not occur in the case of simple indoles[1]. Here we report further reactivity of the activated indoles towards indoloquinone formation. Also new series of activated 2-substituted dimethoxy activated benzimidazole and benzothiazole heterocyclic ring systems (1-4) have been synthesized. These also show interesting chemical reactivity in the benzene ring. A variety of reactions including formylation, acylation, halogenation, nitration, acid catalyzed addition of aldehyde and metal complex formation will be demonstrated. This new reactivity has led to the synthesis of new heterocyclic classes of compounds.



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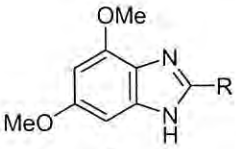

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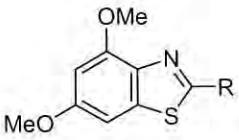

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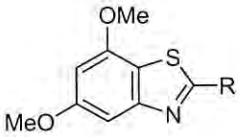

4

References:

Black, D. St. C.; Bowyer, M. C.; Catalano, M. M.; Ivory, A. J.; Keller, P. A.; Kumar, N.; Nugent, S. J. *Tetrahedron*, 1994; *50*, 10497-10508

TP04

N-SUBSTITUTED FLUOROQUINOLONES AS POTENTIAL DUAL ACTION DRUGS TO TREAT RESISTANT BACTERIA.

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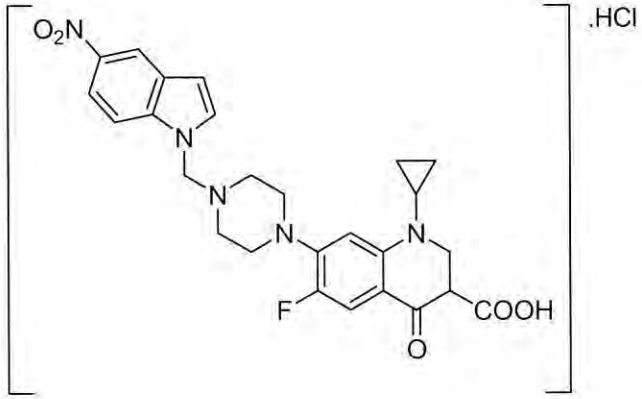
[b]*Department of Biology and Antimicrobial Discovery Center, Northeastern University, Boston, Massachusetts 02115,*

As we progress further into the 21st century, the development of a deadly "superbug" which is resistant to all know antibiotics is becoming more and more a reality and there is a pressing need to develop "miracle drugs for superbugs". One of the clinically significant mechanisms by which bacterial resistance manifests itself is through bacterial efflux pumps which have the ability to extrude a wide range of antibiotics (e.g. β-lactams, ciprofloxacin). A novel way to overcome this form of drug resistance is through the administration of 'efflux pump inhibitors'[1] which can restore antibacterial action in resistant organisms.

The problem with dual drug delivery (administration of an antibiotic and efflux pump inhibitor) is that there is no guarantee, because of differing pharmacokinetics, that both drugs will reach the site of action at the same time.[2] A more exciting and innovative concept is in the design and synthesis of dual action drugs. This concept involves the linking of a known antibiotic to an efflux pump inhibitor *via* a non-cleavable linkage. This poster will cover the development of several novel, and potential dual action drugs (e.g. (**1**) and (**2**)) for the treatment of certain resistant pathogenic bacteria.

(**1**)



(**2**)

References:
1. Lomovskaya, O., Zgurskayam HI., Totrov, M., Watkins, WJ. *Nat. Rev. Drug Discovery*, 2007, 6, 56-65.
2. Frantz, S. *Nat. Rev. Drug Discovery*, 2006, 5, 881-882.

TP05

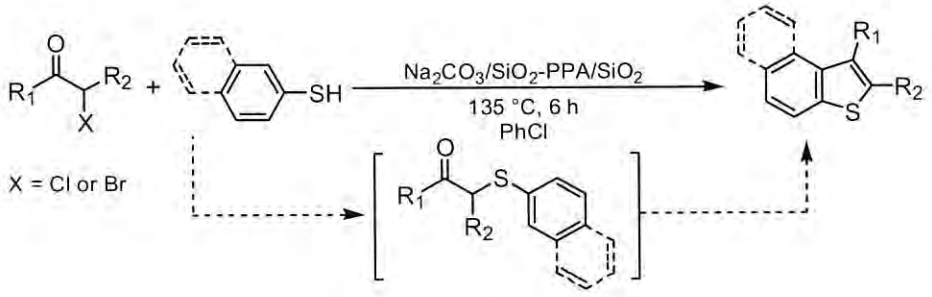
ONE-POT SYNTHESIS OF ARYLTHIOPHENES AND THIOCHROMANS USING SOLID SUPPORTED REAGENTS SYSTEM AS A BASE AND AN ACID

Tadashi Aoyama[1], Hideaki Nakajima[1], Toshio Takido[1]and Mitsuo Kodomari[2]

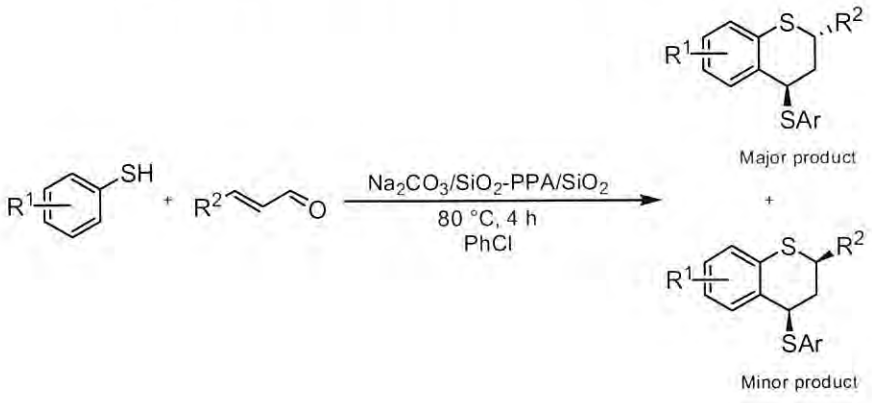
[1]*Department of Materials and Applied Chemistry, College of Science and Technology, Nihon University; Kanda Surugadai, Chiyoda-ku, Tokyo 101-8308, Japan*
[2]*Department of Applied Chemistry, Shibaura Institute of Technology; Toyosu, koto-ku, Tokyo 135-8548, Japan*

Base and acid-catalyzed one-pot synthesis of arylthiophenes and thiochromans using silica gel-supported sodium carbonate (Na_2CO_3/SiO_2) as a base and silica gel-supported polyphosphoric acid (PPA/SiO_2) as an acid has been developed. Both Na_2CO_3/SiO_2 and PPA/SiO_2 can coexist without interacting each other in the same vessel. Therefore, tandem base and acid-catalyzed reactions are able to proceed separately in the same vessel.

One-pot synthesis of benzo[*b*]thiophenes and naphtho[2,1-*b*]thiophenes from aryl mercaptans and α-halo ketones by using Na_2CO_3/SiO_2 and PPA/SiO_2, has been developed. Reaction of α-halo ketones with aryl mercaptans is promoted by Na_2CO_3/SiO_2 to afford α-sulfanyl ketones, followed by cyclization in the presence of PPA/SiO_2 to give the corresponding arylthiophenes. A series of a couple of aryl mercaptanes and α-halo ketones gave the corresponding products in good yields.



2,4-Disubstituted thiochromans were also prepared from aryl mercaptans and α,β-unsaturated aldehydes under similar reaction conditions. Michael addition of aryl mercaptan to α,β-unsaturated aldehyde was promoted by Na_2CO_3/SiO_2, and then the product was cyclized in the presence of PPA/SiO_2. The product which was prepared by using supported reagents system was exclusively *trans*-isomer, whereas the product did not formed stereoselectively when unsupported PPA was used as an acid catalyst.



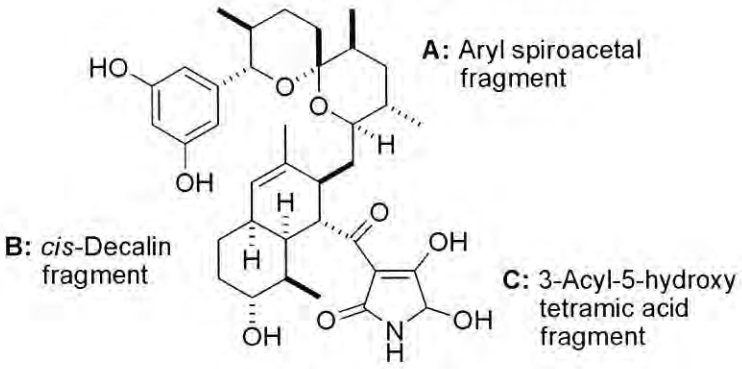
TP06

ANTI-HIV NATURAL PRODUCTS: TOWARDS THE STEREOSELECTIVE TOTAL SYNTHESIS OF INTERGRAMYCIN

Kylee M. Aumann,[a] Fatiah Issa,[b] Mark J. Coster.*,[a]

[a] *Eskitis Institute for Cell and Molecular Therapies, Griffith University, Nathan, QLD, 4111, Australia*
[b] *School of Chemistry, The University of Sydney, NSW, 2006, Australia*

Integramycin was isolated by Singh *et al.* at the Merck Research Laboratories in 2001 from fermentation extracts of the bacteria *Actinoplanes* sp., and was subsequently identified as a novel hexacycle incorporating disparate aryl spiroacetal, *cis*-decalin, and 3-acyl-5-hydroxy tetramic acid fragments (A-C).[1] Biologically, integramycin inhibits the process responsible for incorporating the HIV genome into the host genome, integration, and importantly, does not inhibit human DNA replication. Accordingly, integramycin provides an attractive synthetic target for a new class of anti-HIV pharmaceuticals, the HIV-integrase inhibitors.



Integramycin

Our approach to integramycin relies on the modular disconnection of the molecule into three fragments A-C, allowing for a high degree of convergency, and ultimately an expedient route for synthesizing a range of analogues for structure activity relationship (SAR) studies. Progress towards the aryl spiroacetal subunit A will be reported, including the application of hetero-Diels–Alder methodology to form the spiroacetal moiety, and stereoselective Heck coupling chemistry to install the aryl portion of this subunit.

References:
[1] Singh, SB., Zink, DL., Heimbach, B., Genilloud, O., Teran, A., Silverman, KC., Lingham, RB., Felock, P., Hazuda, DJ., *Org. Lett.*, 2002; 4, 1123-1126.

TP07

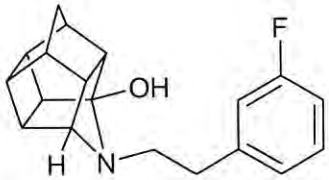
RATTLING THE CAGE: STRUCTURE-ACTIVITY RELATIONSHIPS OF POLYCYCLIC SIGMA RECEPTOR LIGANDS

Samuel D Banister[a], Mark J Coster[b] and Michael Kassiou[a,c]

[a]*School of Chemistry, University of Sydney, Sydney, NSW, Australia*
[b]*Eskitis Institute for Cell and Molecular Therapies, Griffith University, Nathan, QLD, Australia*
[c]*Brain and Mind Reasearch Institute, Camperdown, NSW, Australia*

Sigma receptors have been implicated in the pathophysiology of numerous central nervous system disorders. The elucidation of structure-activity relationships for binding at sigma-1 and sigma-2 receptor subtypes is complicated by the wide structural diversity of known ligands.

It has been shown that compound 1 displays selectivity and a high affinity for sigma-1 receptors (K_i = 10 nM) whilst compound 2 binds sigma-2 receptors selectively (K_i = 20 nM).[1] Compound 1 was recently found to attenuate the effects of cocaine *in vivo*.[2]



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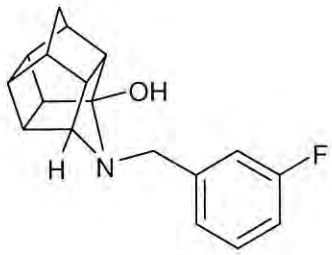

2

Current work is focussed on the synthesis of heteroaromatic analogues of 1 and 2. The synthesis of desoxy derivatives of 1 and 2, to give the corresponding achiral compounds, is also underway.

References:
[1]Liu X, Kassiou M, Christie MJ, Hambley, TW. *Aust. J. Chem.* 2001; 54, 31-36.
[2]Liu X, Banister SD, Christie MJ, Banati R, Meikle S, Coster MJ, Kassiou, M. *Eur. J. Pharmacol,* 2007; 56, 37-42.

TP08

PIRROLO[3,4-*g*]INDAZOLE A NEW RING SYSTEM WITH POTENTIAL ANTITUMOR ACTIVITY

Paola Barraja, Patrizia Diana, Alessandra Montalbano, Annamaria Martorana, Anna Carbone, Girolamo Cirrincione.

Dipartimento Farmacochimico, Tossicologico e Biologico
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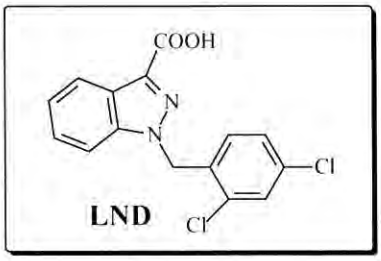
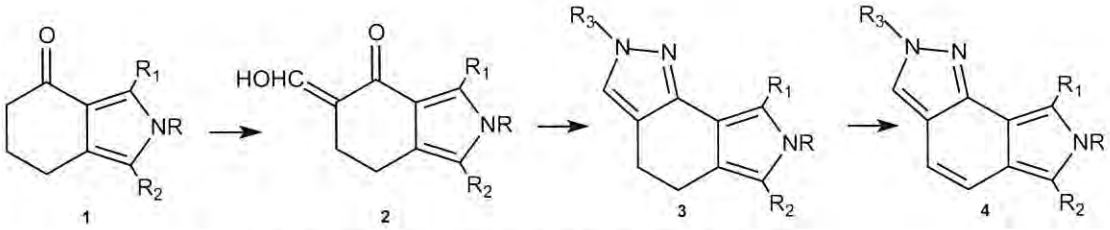
Lonidamine (LND) [1-(2,4-dichlorobenzyl)indazol-3-carboxylic acid] is a potent antitumor agent, tested in clinical trials for the treatment of breast, lung, kidney and bladder tumors acting *via* inhibition of the energy metabolism. It inhibits the oxygen consumption of both normal and malignant cells by blocking the electon-transport chain between primary dehydrogenases and the respiration chain of the mitochondria.[1] Moreover LND acts as a photosensitizer thus potentiating the cytotoxic effect of UV light targeting mainly mitochondria and membrane structures.[2] In the search for new polycondensed heterocycles containing the pyrrole moiety endowed with antitumor activity and being more recently interested in the syntheses of compounds with phototoxic activity[3] we planned the synthesis of the new ring system pyrrolo[3,4-*g*]indazole.
Ketones **1** reacted with ethyl formate and potassium *t*-butoxide in benzene, under nitrogen atmosphere to give in good yields idroxymethylketones **6**. Reaction of **6** with substituted hydrazines in methanol or ethanol furnished in good yields the desired tetrahydropyrrolo[3,4-*g*]indazole derivatives which were in turn dehydrogenated to *pyrrolo[3,4-g]indazole* by treatment with dichlorodicyanobenzoquinone (DDQ). All the synthesised compounds will be subjected to biological screening to evaluate their antiproliferative activity.





R =Me, Bn; R_1= H, Me; R_2= H, CO_2Et; R_3= H, Me, Bn

References: (1) Chekulayev V. et al. *J. Photochem. Photobiol.B*, 1997; 41, 11-21; (2) Floridi A. et al. *Exp. Mol.Pathol.*, 1985; 42, 293-305; (3) Barraja P. et al. *Bioorg. Med. Chem. Lett.*, 2003; 13, 2809-2811; Barraja P. et al. *Bioorg. Med. Chem. Lett.*, 2005; 15, 2291-2294; Barraja P. et al. *Bioorg. Med. Chem.*, 2006; 14, 8712-8728.

TP09

SINTHESIS OF PYRROLO[3,4-*h*]QUINAZOLIN-2-ONE A NEW RING SYSTEM WITH POTENTIAL PHOTOTHERAPEUTIC ACTIVITY

Paola Barraja, Virginia Spanò, Patrizia Diana, Alessandra Montalbano, Annamaria Martorana, Anna Carbone, Girolamo Cirrincione.

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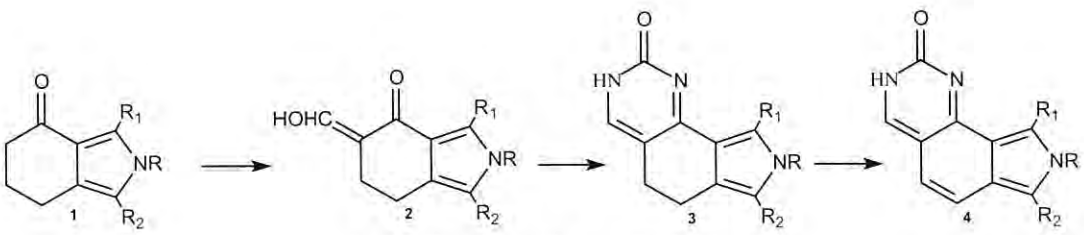
Università degli Studi di Palermo, Via Archirafi 32, 90123 Palermo (Italy)
email: barraja@unipa.it

Linear furocumarins such as Psoralen belong to an important class of photoactivable drugs capable, upon irradiation with UVA light, to intercalate into DNA and photobind with it.[1] With the aim of studying new photoreactive agents with enhanced antiproliferative activity and decreased side effects we recently reported the syntheses of the new ring systems pyrrolo[2,3-*h*]quinolin-2-one and thiopyrano[2,3-*e*]indole whose derivatives showed cytotoxicity higher than shown by 8-MOP (GI_{50} 0.4-16.4 μM and 0.07-2.7 μM respectively).[2] Considering our interest on polycondensed heterocycles with antitumor activity, we planned the synthesis of the new ring system *pyrrolo[3,4-h]quinazolin-2-one*, a pyrroloquinolinone heteroanalogue where an additional nitrogen atom replaces the α-carbon of the pyridone ring. The quinazoline nucleus in fact is part of many antitumor drugs mainly acting as inhibitors of tyrosine kinase receptors. In particular they demostrate to inhibit the growth factor receptors, whose overexpression is associated with aggressive tumour progression.[3]
Our synthetic approach consisted on the annelation of the pyrimidin-2-one ring on the isoindole moiety using hydroxymethylene isoindoles 2 as building blocks, prepared from ketons 1 which were formylated with ethyl formate. Reaction of 2 with urea, acting as dinucleophile, in refluxing anhydrous ethanol afforded the tryciclic derivatives 3. Aromatization of adducts 3 was accomplished with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in refluxing anhydrous toluene. The antitumor activity of the new compounds will be evalutated.



R = Me, Bn R_1= H, Me R_2= H, CO_2Et

References:(1) Comber MF. et al. *Synthesis*, 1992; 731-733 ; (2) Barraja P. et al. *Bioorg. Med. Chem. Lett.*, 2003; 13, 2809-2811; Barraja P. et al. *Bioorg. Med. Chem. Lett.*, 2005; 15, 2291-2294; Barraja P. et al. *Bioorg. Med. Chem.*, 2006; 14, 8712-8728; (3) Palmer BD. et al. *J. Med. Chem.*, 1997; 40, 1519-1529; Gaul MD. et al. *Bioorg. Med. Chem. Lett.*, 2003; 13, 637-640; Hunt JT. et al. *J. Med. Chem.*, 2004; 47, 4054-4059; Rachid Z. et al. *Bioorg. Med. Chem. Lett.*, 2005; 15, 1135-1138.

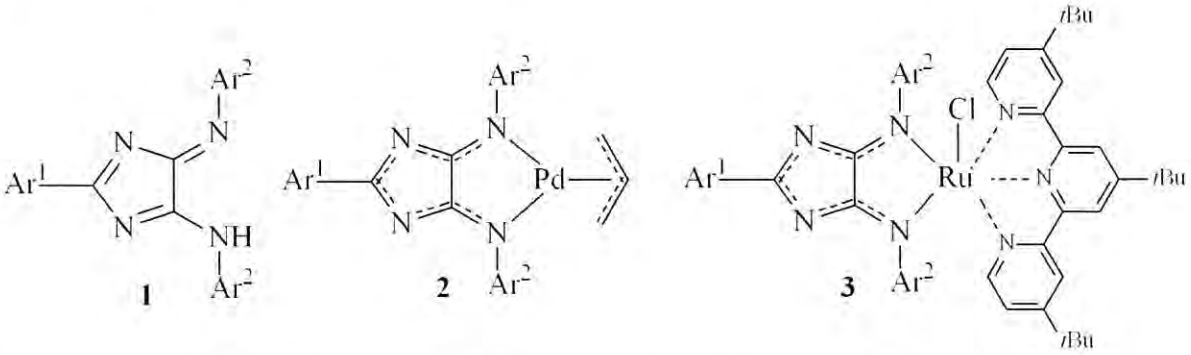
TP10

CHROMOPHORE-LIGANDS FOR PALLADIUM & RUTHENIUM BASED ON 4*H*-IMIDAZOLES

R. Beckert[a]*, J. Blumhoff[a], S. Rau[b*], S. Losse[b]

[a] *Institute for Organic and Macromolecular Chemistry, Friedrich Schiller University Humboldtstrasse 10, D-07743 Jena, Germany*
[b] *Institute for Inorganic and Analytical Chemistry, Friedrich Schiller University August-Bebel-Str.2, D-07743 Jena, Germany*

Apart from porphyrins, phtalocyanines and related systems, metal complexes in which the ligand is identical with an efficient chromophore are quite rare. Our aim was therefore to combine the redox active chromophore of 4*H*-imidazoles 1 with the catalytic activity of selected d-metals. Pd- and Ru-complexes which contain these heterocyclic ligands have been synthesized in good yields. The new Pd-complexes of type 2 can be regarded as new functional dyes as well as deeply coloured and redox active metallacycles which display catalytic activity [1]. In contrast to parent compounds 1, derivatives 2 show two well separated reductions which are fully reversible. The values of semiquinone formation constants of derivatives 2 (between 10^{11} and 10^{12}) are only somewhat lower than those reported for similar boracycles [2]. In view of the heterocycle 1 the complexation reaction is accompanied by a change from a merocyanine to a cyanine-chromophore. Thus, we synthesized novel Ru-complexes which might be applicable as antenna part for light-driven reactions [3].



Complexes of type 3 absorb in their UV/vis-spectra at about 640 nm ($\varepsilon \leq 20000\ M^{-1}cm^{-1}$). Exchange of Ru-coordinated ligands has a pronounced influence on the photophysical properties.

[1] J. Blumhoff, R. Beckert, D. Walther, S. Rau, M. Rudolph, H. Görls, W. Plass, *Eur. J. Org. Chem.* 2007, 481-486.
[2] T. Gebauer, R. Beckert, D. Weiß, K. Knop, C. Käpplinger, H. Görls, *Chem. Commun.* 2004, 1860-1861.
[3] S. Rau, B. Schäfer, D. Gleich, E. Anders, M. Rudolph, M. Friedrich, H. Görls, W. Henry, J. G. Vos, *Angew. Chem.* 2006, 118, 6316-6318.

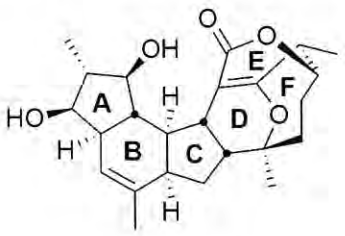
TP11

A TRANSANNULATION APPROACH TO THE SYNTHESIS OF HETEROCYCLIC NATURAL PRODUCT FRAGMENTS

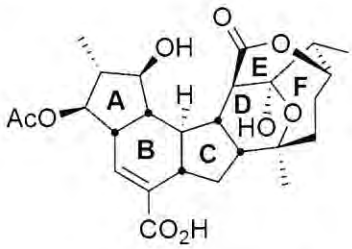
Dr Richard JG Black, Dr Paul Clarke.

School of Chemistry, University of Nottingham, University Park, Nottingham, NG7 2RD, UK.

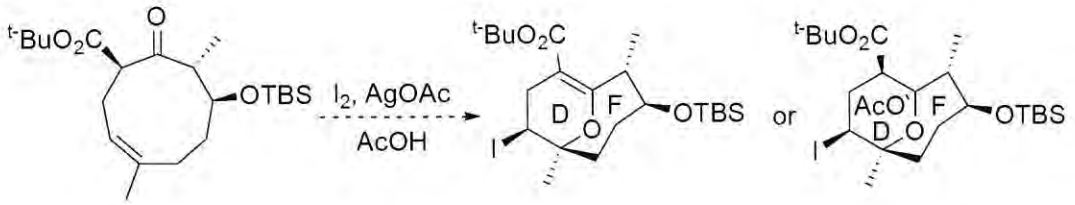
A transannular iodocyclisation of a nine-membered carbocyclic ring was expected to furnish the fused, bicyclic 6,7-ring system of the DF-rings of the structurally comparable natural products FR182877 and hexacyclinic acid, based on a model study.[1]



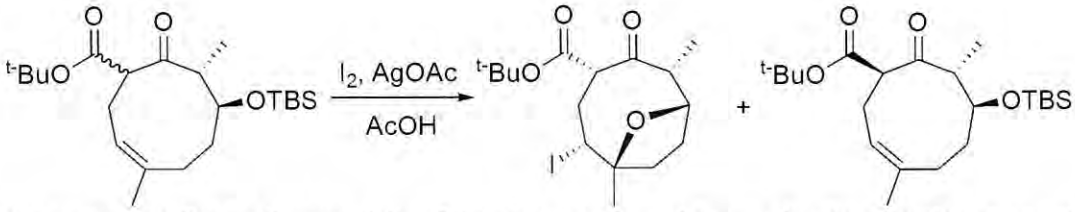
FR182877



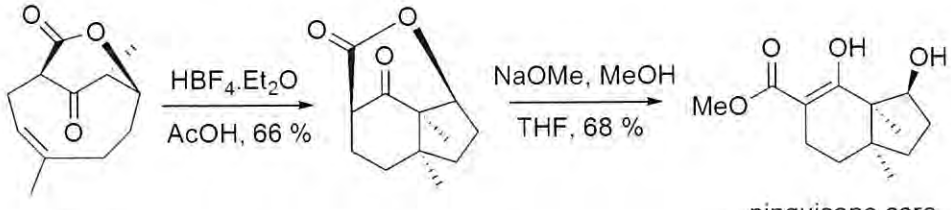
hexacyclinic acid



Instead, submission of an inseparable mixture of diastereomers of the nine-membered ring to the reaction conditions demonstrated a competing mode of cyclisation giving an undesired 5,8-ring system only.



Subsequent studies on the reactivity of the nine-membered ring and various analogues gave rise to bicyclic and tricyclic ring systems, none of which showed the desired cyclisation. However, a novel route to the bicyclic core of the pinguisane family of sesquiterpenoids was uncovered from a bicyclic lactone intermediate by way of a Brønsted acid promoted transannular enol alkylation, followed by base induced lactone opening.[2]



pinguisane core

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TP12

DESIGN & EVOLUTION OF INHIBITORS OF DIHYDRODIPICOLINATE SYNTHASE (DHDPS).

Boughton, Berin A.[1], Gerrard, Juliet A.[2], Hutton, Craig A.[1]

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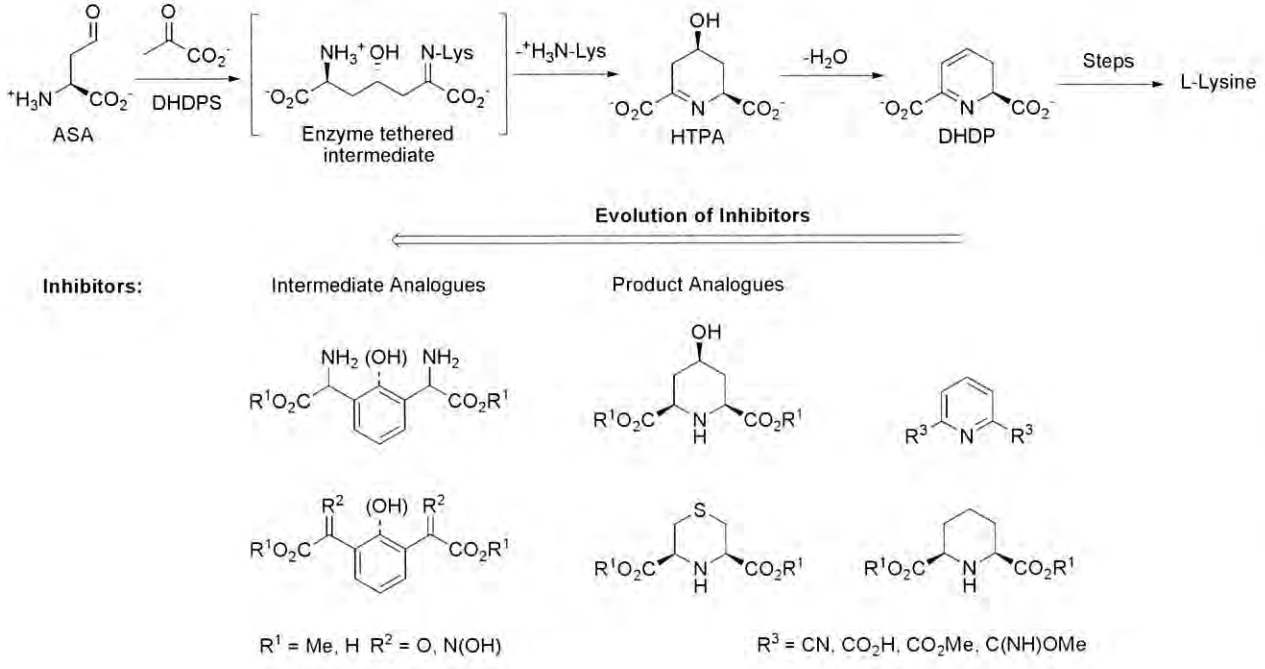
[2] *School of Biological Sciences, The University of Canterbury, Christchurch, New Zealand*

The L-lysine biosynthetic pathway[1] has attracted considerable attention as a target for the design of new antibiotics. The two products from this pathway, lysine and its immediate precursor *meso*-diaminopimelate (*meso*-DAP), are essential components of the bacterial peptidoglycan[2] and removal of either leads to rapid cell death.[3] The initial and rate limiting step towards the biosynthesis of lysine involves the condensation of pyruvate and aspartate semi-aldehyde (ASA) catalysed by the enzyme dihydropdipicolinate synthase (DHDPS), to form 4-hydroxytetrahydrodipicolinate (HTPA).[4] HTPA undergoes spontaneous dehydration to give dihydrodipicolinate (DHDP), which then undergoes a series of enzyme-catalysed reactions to give lysine. Traditionally, inhibitors of DHDPS have been designed as either simple substrate or product analogues. Herein, we discuss the evolution of design strategies from these simple beginnings to our current design strategy reporting the effectiveness of inhibitors within each successive class.



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TP13

APPLICATION OF THE PINHEY-BARTON ORTHO-ARYLATION TO THE TOTAL SYNTHESIS OF ANCISTROTANZANINE A

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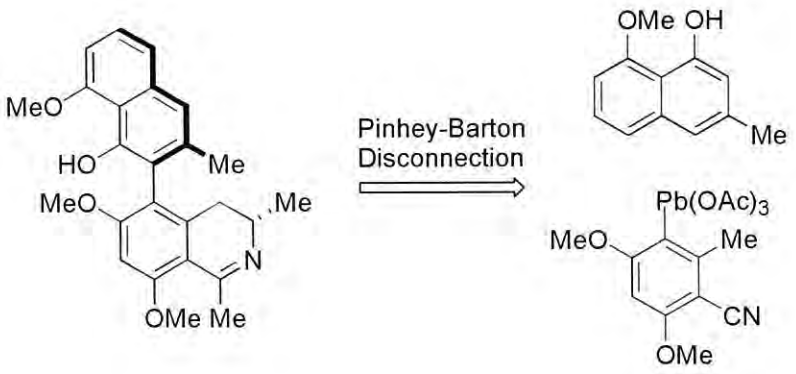
Extracts from the tropical Ancistrocladaceae and Dionophyllaceae plant families have been used in traditional medicines for the treatment of malaria and dysentery.[1] Recent examinations of these extracts have revealed that the profound biological activity is due to the presence of naphthylisoquinoline alkaloids. There are significant challenges in the synthesis of these compounds, particularly in the generation of the highly hindered tetra-substituted biaryl bond in an atroposelective fashion.

The Morris group have pioneered the use of the Pinhey-Barton reaction to prepare such biaryl bonds.[2] Application of this strategy is being used to prepare ancistrotanzanine A, in an atroposelective fashion.[3]



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TP14

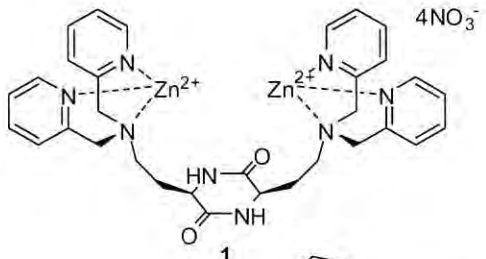
SYNTHETIC PEPTIDES BEARING DIPICOLYLAMINO SIDEARMS: ANION RECEPTORS

Stephen J. Butler, Katrina A. Jolliffe

School of Chemistry, The University of Sydney, 2006, NSW, Australia

The development of synthetic peptides as scaffolds for anion recognition and enzyme mimics is of current interest. The use of synthetic peptides allows a range of functional groups to be displayed in a spatially well defined fashion, preorganised for binding a target guest[1]. Anions such as pyrophosphate ($P_2O_7^{4-}$, PPi) and adenosine triphosphate (ATP) play important roles in a variety of metabolic processes, and to this end biomedical science is able to apply the selective detection of these anions in a variety of tasks.

We present here the synthesis of a series of novel cyclic peptides (eg. **1** and **2**) of different sizes, functionalized with zinc(II)dipicolylamino sidearms, and demonstrate that these compounds bind selectively to biologically significant anions.



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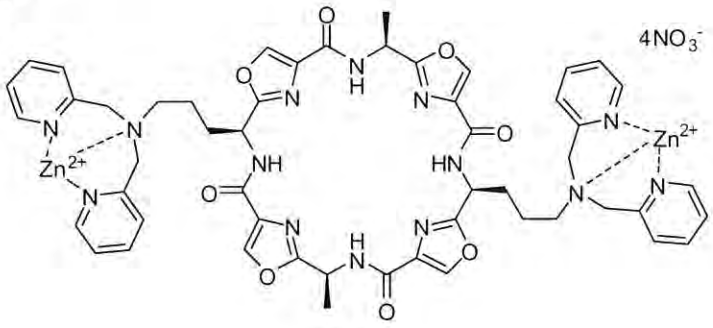

2

References:

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TP15

EFFICIENT SYNTHESIS OF 4,5-DISUBSTITUTED-2-AIMINOIMIDAZOLES USING MICROWAVE IRRADIATION

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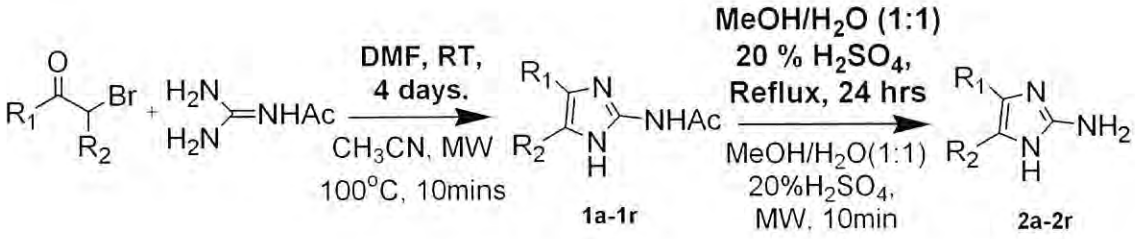
A library of 4,5-disubstituted-2-aminoimidazoles was synthesized using microwave irradiation. The reaction between α-haloketones and N-acetylguanidine yielded 4,5-disubstituted N-(1H-imidazol-2-yl) acetamides, 1 which were then hydrolyzed into their corresponding 4,5-disubstituted-2-aminoimidazoles, 2. Compared to traditional solution-phase methodologies, the percentage yields of 2 obtained via microwave synthesis were significantly higher and the reaction times were greatly reduced from 6 days[1] to 20mins.



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TP16

STUDIES TOWARDS THE SYNTHESIS OF CYCLIC PEPTIDE MIMETICS DERIVED FROM *N*-ACYLISATINS

Wai Ching Cheah, David StC Black, Naresh Kumar

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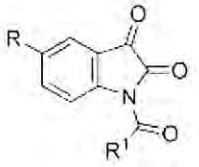
Email: elainew.cheah@gmail.com

Peptidomimetics are non-peptide molecules that are capable of mimicking and antagonizing the biological action of a natural parent peptide. As a part of an ongoing project investigating the synthesis of peptide mimetics derived from *N*-acylisatins 1, a series of bis-glyoxyamides 2 has been synthesized and subjected to ring closing metathesis and EDC coupling reactions respectively. This paper will outline methodologies for the synthesis of bis-glyoxyamides 2 and attempted cyclisation reactions.



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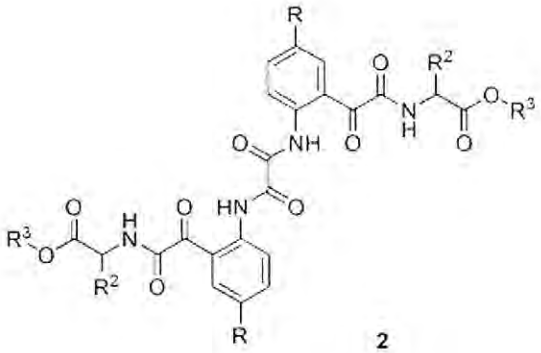


2

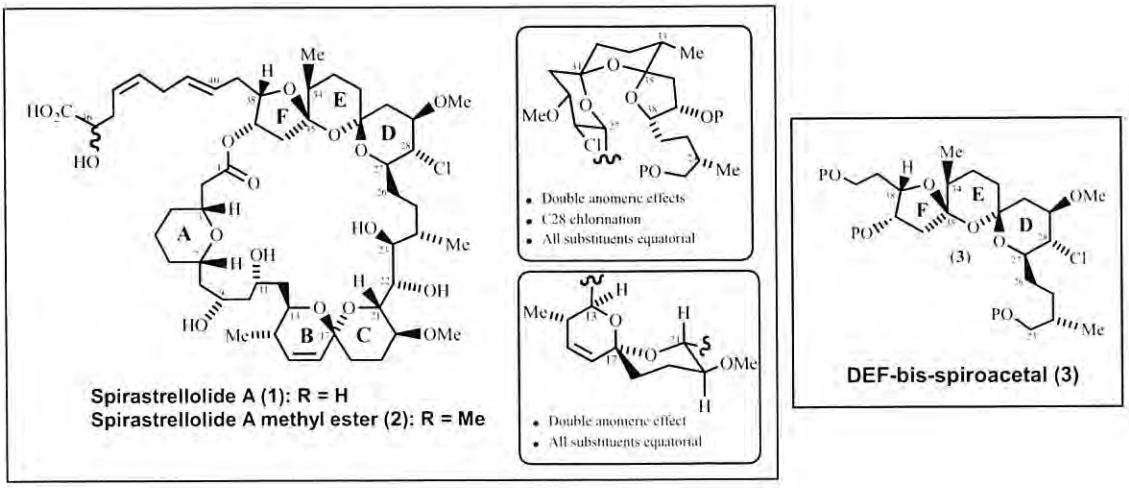
TP17

SYNTHETIC STUDIES TOWARDS THE DEF BIS-SPIROACETAL RING SYSTEM OF SPIRASTRELLOLIDE A

Jack L. Y. Chen and Margaret A. Brimble

Department of Chemistry, University of Auckland,
23 Symonds St, Auckland.

Spirastrellolide A 1 is a novel macrolide recently isolated from extracts of the Caribbean marine sponge *Spirastrella coccinea*.[1] Both the crude *S. coccinea* extract and the pure methyl ester 2 of spirastrellolide A have shown potent activity in a cell-based assay for antimitotic activity.[2] However, unlike antimitotic sponge macrolides in the spongistatin, laulimalide, peloruside and halichondrin families, spirastrellolide A does not affect tubulin polymerization *in vitro*. Spirastrellolide A acts as a potent (IC_{50} = 1 nM) and selective inhibitor of protein phosphatase 2A (PP2A), believed to suppress tumour development by causing premature entry of cells into mitosis, prior to causing mitotic arrest of the cell.[3] Spirastrellolide A contains a 47-carbon linear polyketide backbone incorporated into a highly functionalized 38-membered lactone containing a tetrahydropyran ring, a bicyclic spiroacetal ring system and a tricyclic bis-spiroacetal ring system. Herein, we report progress towards the synthesis of the intriguing chlorinated 5,5,6-bis-spiroacetal DEF ring system 3 of spirastrellolide A.



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TP18

SYNTHESIS OF SULFUR-SUBSTITUTED QUINOLIZIDINE DIENES BY ENYNE METATHESIS AND STUDY OF THEIR [4+2〕CYCLOADDITION REACTIONS

Shang-Shing P. Chou,* and Chih-Chun Chang

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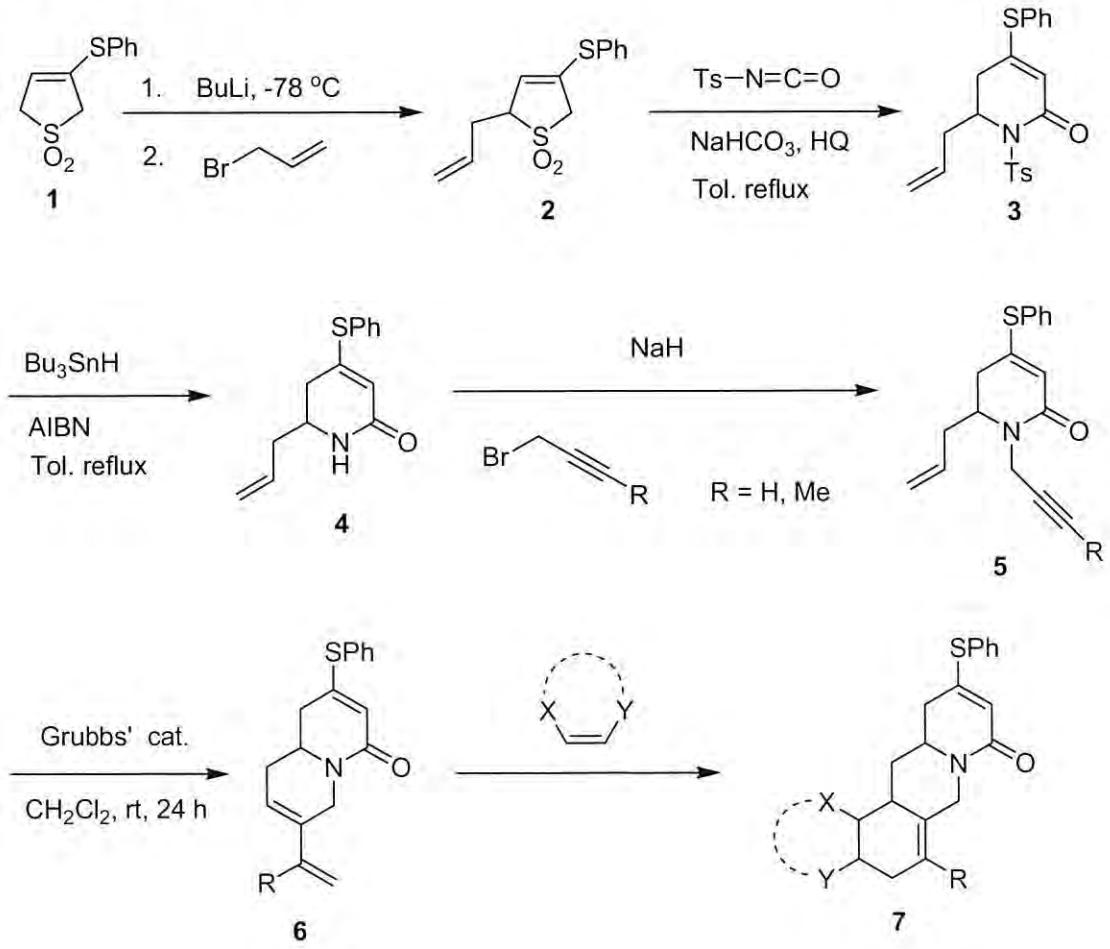
We have previously reported the synthesis of lactam 4 from 3-sulfolene 1.[1-2] We have now converted 4 to the quinolizidine dienes 6 by enyne metathesis (RCEYM).[3] We have also studied the [4+2] cycloaddition reactions of 6 with some dienophiles to give products 7 with new heterocyclic structures.



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[1] Chou SSP.; Hung CC. *Tetrahedron Lett.* 2000; 41, 8323-8326.
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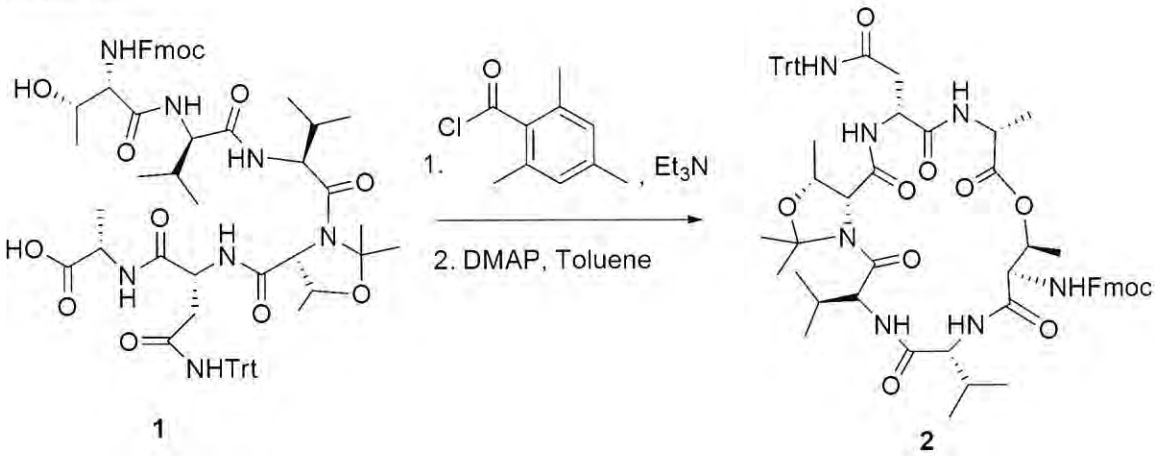
TP19

TOWARDS THE SYNTHESIS OF LI-F ANTIFUNGAL CYCLIC PEPTIDES

James Cochrane, Katrina A. Jolliffe.

School of Chemistry, University of Sydney.

The LI-F antibiotics are cyclic depsipeptides consisting of a hydrophobic cyclic core with an alkyl chain attached externally. They have been found to exhibit strong antifungal and antibacterial activity.[1] This is of interest as fungal infections are becoming an increasing world health problem due to the growth in the immunocompromised population. There are also limitations with the available antifungal treatments due to their toxicity and the development of resistance.[2]



1 2

The protected cyclic core of LI-F04a (2) was synthesised by cyclising the linear hexapeptide (1) using Yamaguchi lactonization conditions. The solution phase synthesis of 1 was achieved in 3 % overall yield in 17 steps. The peptide contains the amino acid residue D-*allo*-threonine. This had to be synthesised from D-threonine. This residue was further functionalised by the formation of a pseudoproline. These heterocycles have been shown to aid in the cyclisation of peptides by inducing a *cisoid* amide bond, especially when the heterocycle is 2C, 2C dimethylated. Pseudoprolines are believed to act as a hinge within the molecule facilitating cyclisation.[3]

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TP20

EASY ACCESS TO NEW HETEROCYCLIC SYSTEMS: [1,4]-OXAZINE AND SUBSTITUTED [1,4]-OXAZINES

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ICOA, UMR 6005, Université d'Orléans, BP 6759, 45067 Orléans cedex 2, France

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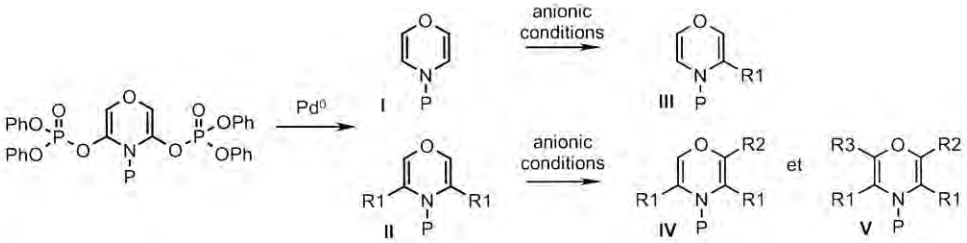
Enol phosphates represent versatile intermediates in the construction of complex organic molecules.[i] The ability to easily convert enol phosphates into a myriad of functional motifs of synthetic relevance is well known. In particular, this moiety has proved to be a robust and versatile precursor for a number of cross-coupling reactions facilitated by Pd(0) and Ni(0). Enol phosphates have in fact, in a few cases, proved to work better in cross-coupling reactions than their triflate counterparts owing to higher stability, higher yield and easier work up. The ability of enol phosphates to undergo these cross-coupling reactions in the presence of various heteroatoms, makes them attractive functional groups for the construction of various substituted heterocyclic systems.

In previous reports,[ii] we have outlined the synthesis of 2,6-disubstituted 1,4-dihydropyridines from imides derivatives by way of Pd-catalyzed coupling reaction of the corresponding *bis*-vinylphosphates. In this study, we explored the possibility of synthesizing 1,4-oxazine and its corresponding 3,5-disubstituted derivatives by the same method. We considered then functionalizing these new scaffolds under anionic conditions to get easy access to mono-, tri- and tetrasubstituted 1,4-oxazines with diversity on the side chains.[iii]



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[1] (a) Mousset, D. ; Gillaizeau, I.; Hassan, J.; Lepifre, F.; Bouyssou, P. ; Coudert, G. *Tetrahedron Lett.* **2005**, *46*, 3703. (b) Mousset, D.; Gillaizeau, I.; Sabatié, A.; Bouyssou, P.; Coudert, G. *J. Org. Chem.* **2006**, *71*, 5993.

[1] Claveau, E. ; Gillaizeau, I. ; Blu, J. ; Coudert, G. *J. Org. Chem.* **2007**, *72*, 4832.

TP21

REGIOSELECTIVE N_1-ALKYLATION OF 4-QUINOLONE-3-CARBOXYLIC ACID ESTERS USING MODIFIED MITSUNOBU REACTION

Zohreh Amoozgar and Mohsen Daneshtalab

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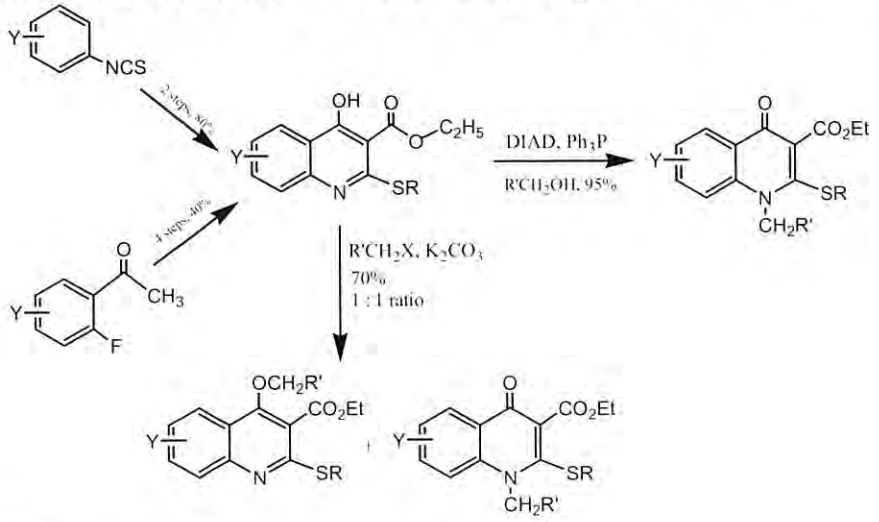
E-Mail: *mohsen@mun.ca*

Quinolin-4(1*H*)-one-3-carboxyxlic acid derivatives (quinolones) have been known as potent inhibitors of prokaryotic and eukaryotic Topoisomerase II enzymes for decades. As inhibitors of prokaryotic topoisomerase II (DNA gyrase and topoisomerase IV), quinolones have been widely used for the treatment of severe bacterial infections in the past two decades. Inhibitors of eukaryotic topoisomerase II have recently been introduced as potential antitumor agents. Hundreds of reports in respect to the syntheses and reactivity of quinolones have been published so for, among which those based on Gould-Jacobs reaction and its modified procedures are of global use. The most challenging step in the syntheses of N_1-substituted-quinloin-4(2*H*)-one-3-carboxylates is the regioselective alkylation of the N_1-position using an alkyl halide as the alkylating agent. In this respect, two isomeric products, N_1-alkylated and C_4-*O*-alkyalted products are indiscriminately formed, of which the N_1-alkylated product is required. Another approach in obtaining pure N_1-alkylated isomer is the direct synthesis of this isomer via an *o*-halo-benzoylacetate ester derivative that is allowed to react with and appropriate alkylisothiocyanate followed by cyclization to the target compound. Although in the former procedure a variety of N_1-alkylated quinolones can be prepared using quinolin-4(1*H*)-one-3-carboxyxylate as a building block, the non-selectivity of reaction results in isolation problem and the low yield of the required product. The latter procedure, despite production of the required isomer, does not seem feasible if the objective of synthesis is preparation of compounds with diverse alkyl substituents at the N_1-position. In order to overcome this problem, we developed a method based on Mitsunobu alkylation of compounds using appropriate alkyl alcohols. Indeed, *N*-alkylation of 1*H*-indazole and 9*H*-carbazole, maleimides , 3,4-dihydro-pyrimidin-2(1*H*)-ones, and several other heterocyclic systems via Mitsunobu reaction have been reported (1-3). In this presentation, we would like to report a regioselective N_1-alkylation of a series of 2-alkylmercaptoquinolin-4(1*H*)-one-3-carboxylates using a modified Mitsunobu reaction. The yield of the products, based on the 2-alkylthio precursor was 95-98%, as depicted in the following scheme.



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(2) Dallinger D, Kappe O. *Synlett*, 2002, 1901-1903

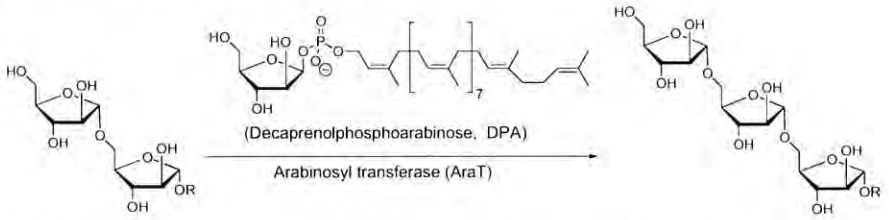
TP22

SYNTHESIS OF AZASUGARS FOR THE TREATMENT OF TUBERCULOSIS

Emma Dangerfield,[1] Mattie Timmer,[2] Joanne Harvey,[2] and Bridget Stocker[1,2]
[1] *Malaghan Institute of Medical research*
[2] *Victoria University of Wellingtion*

Tuberculosis (TB) is one of the greatest infectious disease scourges in the world today. Two billion people are infected with *Mycobacterium tuberculosis,* the pathogen that is responsible for TB. Current treatments for TB have limited efficacy due to the emergence of drug resistant strains.[1] *M. tuberculosis* possess an extraordinarily thick cell wall that protects the organism from its environment. Key structural components of the mycobacterial cell wall include the two polysaccharides, arabinogalactan (AG) and lipoarabinomannan (LAM).[2] Significant effort in the quest for new anti-mycobacterial agents has been spent on identifying compounds that inhibit enzymes involved in cell wall biosynthesis.[3]

Arabinosyl transferases (AraT) play a critical role in the construction of the *M. tuberculosis* cell wall. These enzymes catalyse the glycosylation reactions that build up the arabinan sugar chains found in both AGs and LAMs.[4] In these glycosylation reactions the arabinose donor is often decaprenolphosphoarabinose (DPA). A prototypical AraT-catalysed reaction, involving the coupling of an oligosaccharide acceptor with the DPA donor to afford an elongated oligosaccharide, is given in scheme 1. Mammals do not possess AraTs and hence these enzymes are ideal targets for drug action.



Scheme 1: A prototypical Arabinosyl transferase catalysed reaction

The goal of our research is to synthesise novel azasugars for use as inhibitors of AraTs and other enzymes involved in *M. tuberculosis* cell wall biosynthesis. These derivatives will also aid our understanding of AraT-catalysed glycosylations in *M. tuberculosis* and facilitate the development of broad-range, anti-mycobacterial therapeutics.

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4. a) Lee, RE; Mikusová, K; Brennan, PJ; Bersa, GS. *J. Am. Chem. Soc.* 1995, *117*, 11829-11832. b) Lee, RE; Brennan, PJ; Bersa, GS. *Glycobiology* 1997, *7*, 1121-1128.

TP23

A MODIFIED ROUTE TO SILDENAFIL

Noël Hosten, Pierre J. De Clercq

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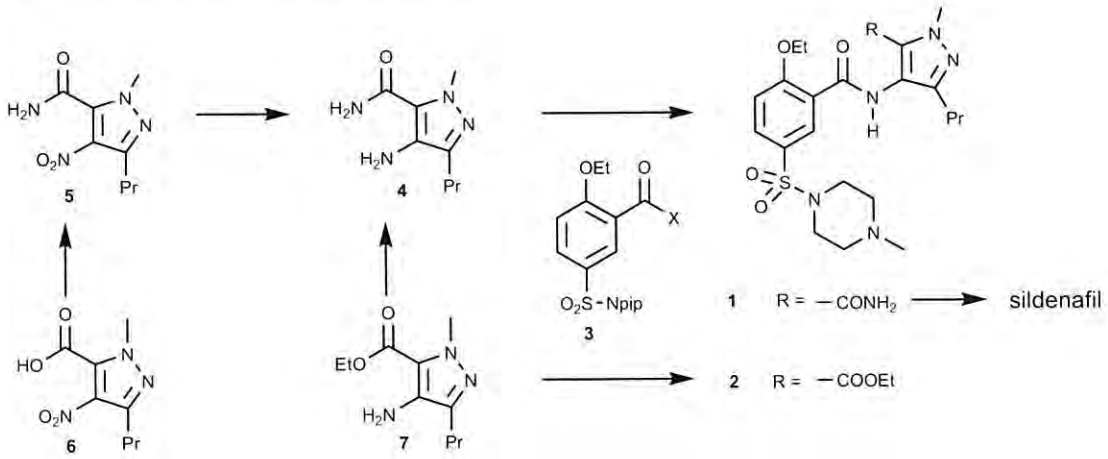
In search of an attractive project for the undergraduate laboratory we have considered the convergent synthesis of sildenafil, the well-known phoshodiesterase(V) inhibitor (sildenafil citrate is the active ingredient in Viagra™).[1] In the optimised sequence,[2] the pyrimidinone ring of sildenafil is generated through cyclisation of amide 1 (KO^{t}Bu, anhydrous ^{t}BuOH, 100%), which is obtained via acylation of an activated sulfonamide acid derivative (3) with aminopyrazole 4. The latter can be obtained from acid 6 after acid activation and ammonolysis to 5 followed by reduction of the amino group.[3]

In view of the hazard posed by the nitration step involved in the synthesis of 6,[2] we rather considered an alternative sequence that has been described in the context of the use of polymer-supported reagents for multi-step organic synthesis,[4] in which amino ester 7 is an important intermediate.[5] In our hands, however, simply dissolving 7 in a saturated solution of ammonia did not yield the required 4.[6] As an alternative amino ester 7 was coupled with activated 3 (ClCOOEt, Hünig's base) to yield 2 (55%). The latter was eventually converted to 1 using dimethylaluminum amide (81%).[7]



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TP24

NEW SYNTHETIC HETEROCYCLIC BIOACTIVE MOIETIES AND STUDIES OF THERE ANTICANCER AND ANTIMICROBIAL ACTIVITY

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Heterocyclic compounds arose on our planet long before the first living creatures. Together with other classes of organic compounds, heterocyclic compounds promoted the formation of life on Earth. Nature selected the heterocycles, as the basis of the most essential biological systems. Heterocyclic compounds are widely distributed in nature are essential to life; they play a vital role in the metabolism of all living cells. There are a waste number of pharmacologically active heterocyclic compounds, many of which are in regular clinical use. There is no doubt that the chemistry of heterocycles will continue to grow for the creation of new drugs, agrochemicals, novel materials, etc. In our laboratory we have synthesized large variety of heterocyclic compounds which exhibited interesting anticancer, antituburcular and antibacterial activity.

The practice of medicinal chemistry is devoted to the discovery and development of new chemical entities used as medicinally important leads. The mission of drug research is to discover new drugs, which can be used as tools to cure of prevent disease. The past few decades have witnessed a significant increase in the microbial diseases. The infection caused by different microorganisms like bacteria, fungi, virus has affected human beings as well as animals. Hence, this class of drugs is the greatest contribution of the 21st century to Medicinal chemistry.

A wide variety of biological activities of 2-amino thiazole derivatives have prompted to us to synthesize some imine derivatives,β-lactum, 4-thiazolidione derivatives and study their antimicrobial activities. The following compounds were found to have anticancer activities. 4-chloro-3-methoxy-N-[4-{2-(phenyl imine)-1,3-thiazole-4yl}phenyl]benzene sulphonamide. 4-chloro-N-[4-{2-(-3-chloro-2-phenyl-4-oxo-1-azetidinyl)-1,3-thiazole-4yl}phenyl]benzene sulphonamide. 4-chloro-3-methoxy-N-[4-{2-(phenyl-4-oxo-1,3-thiozolidine-3-yl)-1,3-Thiazole-4yl}phenyl] benzene sulphonamide. Moreover Quinazolone exhibits an important role in producing

β-blockers. In our search for higher activities the following Quinazolone and oxo-azetidines compounds were synthesized and screened for anticancer activities. 2-[4(2'4'-dichlorophenoxy)-phenoxy methyl]-3-(4'-{4'-chloro, 3"-chloro diphenyl ether }-6-sulpho-4-oxo Quinazoline. 2-methyl-3-(4-chloro phenyl thiourea)-6-nitro -4-oxo Quinazoline and 4-(-3'-chloro phenyl)-1-N-{4"-(2"-mercapto-4"oxo Quinazoline) phenyl } 2-oxo azetidinone. Similarly benzobisthiazole compound were synthesized and screened for their anticancer activity. The constitution of the products have been supported by elemental analysis, IR spectral studies.

TP25

PALLADIUM-CATALYSED CYCLISATION OF AMINE DERIVATIVES

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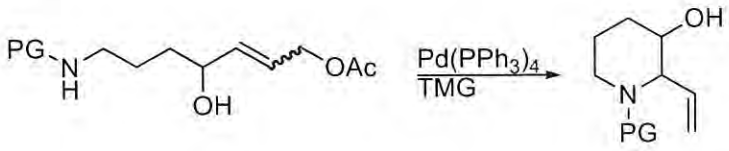
Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyany Technological University, Singapore 637616, Singapore.

The preparation of heterocycles are of significant importance to the modern day synthetic chemist and have attracted a large amount of attention due to their presence in a whole host of natural products and the biological properties associated with them. We have utilized a π-allyl palladium interaction to elegantly create a piperidine ring system. The reaction shows high stereoselectivity. Our results and applications will be presented.



TP26

ON THE DEVELOPMENT OF RECYCLABLE HYPERVALENT IODINE(III) REAGENTS BASED ON THE TETRAHEDRAL STRUCTURES

Toshifumi Dohi, Akinobu Maruyama, Naoko Takenaga, and Yasuyuki Kita

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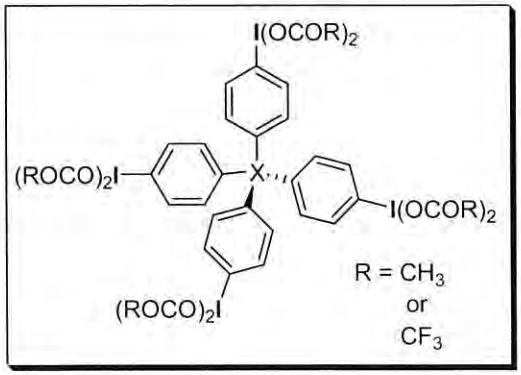
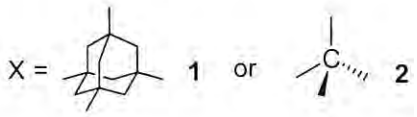
Hypervalent iodine(III) compounds such as phenyliodine(III) diacetate (PIDA) and phenyliodine(III) bis(trifluoroacetate) (PIFA) are recognized as one of the promising, useful and safe oxidation tools showing mild oxidation ability which allows oxidative transformations in high yields and with high functional selectivity. Recent advance for utilization of recyclable hypervalent iodine(III) reagents toward many organic transformations also enhances their significance. As a result, polymer-supported hypervalent iodine(III) reagents are widely used as the useful and environmentally benign tool as the result of their simple operation and recyclability. However, the conventional polymer-supported reagents still have several drawbacks such as difficulty for controlling the loading efficiency, degradation loss of resin by repeated use, lower reactivity compared to the corresponding monomeric reagents PIDA and PIFA, and so on. Thus, design and synthesis of new recyclable hypervalent iodine reagents have been actively investigated these days.

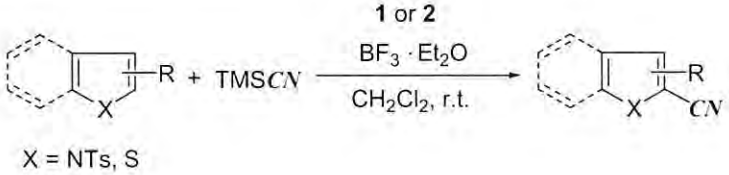
Recently, we have developed a novel recyclable and non-polymeric hypervalent iodine(III) reagent 1 and its analogue 2 having the tetrahedral structures.[1] In some oxidation reactions, we found that these reagents have excellent reactivities similar to those of PIDA and PIFA as well as high recyclabilities enough to overcome the drawbacks of previous polymer-supported iodine(III) reagents. The advantageous features of the reagents are considered to be highly dependent on their unique structures. Further investigation on the scope and structural elucidation of the new recyclable reagents will be presented in the poster session.

New Useful Alternatives to PIDA and PIFA



1) *High reactivity* in various solvents
2) *High recyclability* without degradation loss
3) *Simple operation* (solid-liquid separation)
4) *Easy preparation*
5) *High stability*





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TP27

A DIVERGENT APPROACH TO THE SYNTHESIS OF PYRANONAPHTHOQUINONE ANTIBIOTICS

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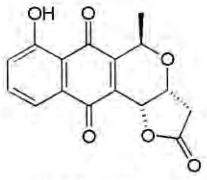
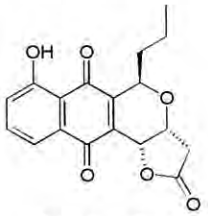
Members of the pyranonaphthoquinone family of natural products exhibit a diverse array of biological activities.[1] Examples include kalafungin 1 (inhibitor of pathogenic fungi, protozoa and yeasts), frenolicin B 2 (antifungal and anticoccidial activity) and arizonin B1 3 (antimicrobial activity against pathogenic strains of Gram-positive bacteria). It has been proposed that the mechanism of action of these natural products involves formation of a reactive *ortho*-quinone methide alkylating species.[2] Alternatively, their bioactivity may result from free radical-induced damage through redox cycling, a process well recognized in quinone systems.[3]

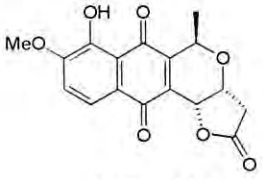
We are developing a divergent, stereospecific synthesis of pyranoquinones that will allow numerous members of this family to be prepared, including the natural products 1-3. This should provide the opportunity for a thorough structure-activity profile to be established and enable the mode of action of these compounds to be investigated.



Kalafungin **1**



Frenolicin B **2**



Arizonin B1 **3**

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TP28

FURANO-DENDRALENES

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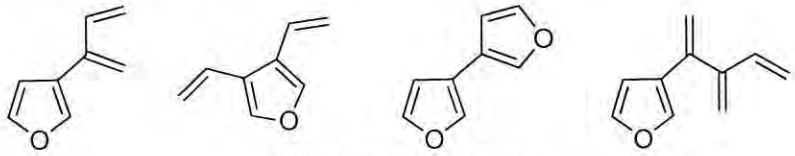
Practical methods for the synthesis of the dendralene family of fundamental hydrocarbons have recently been developed within the Sherburn Group and their Diene-Transmissive Diels-Alder (DTDA) chemistry has been demonstrated.[4] This work focuses on the synthesis and development of DTDA sequences of a range of dendralenes incorporating a furan ring within their structure. The inclusion of this furan ring has the potential to allow control of site selectivity as well as *endo/exo* selectivity in Diels-Alder cycloadditions. The DTDA sequences of these furanodendralenes may allow access to highly complex oxygenated ring systems, which may serve as intermediates in the synthesis of natural products.



Furanodendralenes

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TP29

SYNTHESIS OF NEW b-CARBOLINE ANALOGUES

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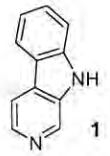
E-mail: Anne.Fiksdahl@chem.ntnu.no

β-Carboline (1) is a natural product of great interest due to the biological activity and pharmacological properties of a series of its derivatives.



1

A method aiming at the preparation of new sulphur-, oxygen- and nitrogen-containing β-carboline analogues has been studied.

A synthetic strategy for the preparation of new b-carboline analogues 3 from pyridine will be discussed. Nitropyridines are now readily available through an improved nitration method [1].

Three essential steps were:

Suzuki cross-coupling

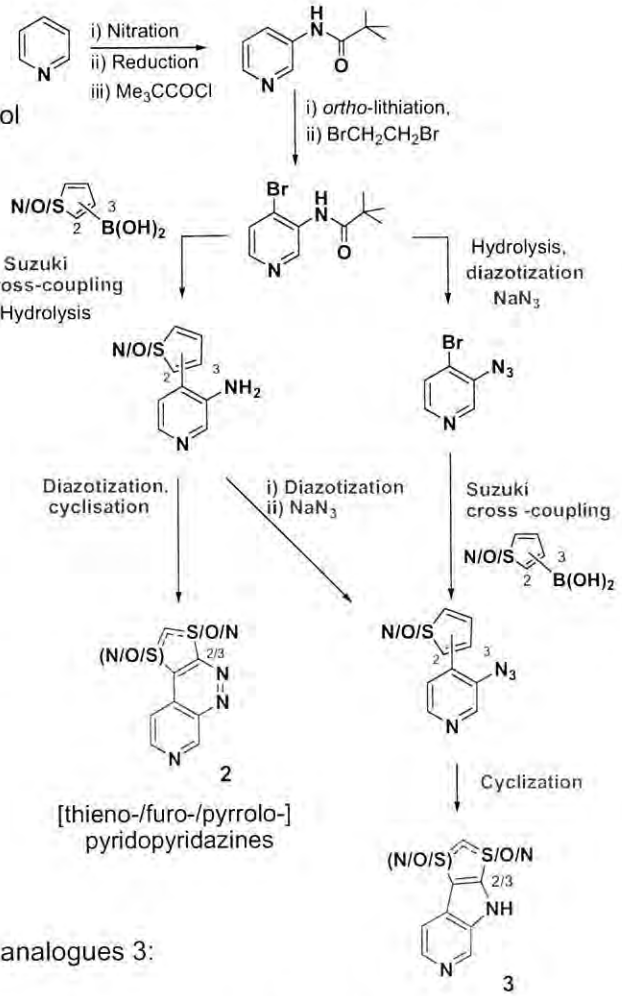
of the appropriate thiophene / furan / pyrrol 2- or 3-boronic acids and bromopyridine substrates afforded biaryl intermediates.

Diazotisation / azide nucleophilic substitution

afforded the azide precursors.

Due to the electronrich character of thiophene / furan / pyrrol, these reactions also could afford new pyridazine diazocoupling products 2

The order of reactions could be exchanged to obtain yield optimalisation for specific products.



[thieno-/furo-/pyrrolo-] pyridopyridazines

Cyclisation

Thermal decomposition of the azide precursors afforded the new b-carboline analogues 3:

β -Carboline analogues
[thieno-/furo-/pyrrolo-]pyrrolopyridines

References:
[1] Bakke, J. M.; Ranes, E. *Synthesis*. 1997; 283.

TP30

SYNTHESIS AND PHOTOCHROMIC PROPERTIES OF 3,4-DI(HETEROARYL)COUMARINS

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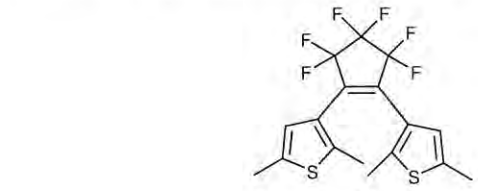
b Department of Chemistry, University of Southampton,Southampton SO17 1BJ, UK

The literature covering diarylethene photochromic systems whilst very extensive [1] has centred on systems containing perfluorocyclopentene *e.g.* 1 or maleic anhydride/maleimide *e.g.* 2 bridging units. Few systems in which the alkene moiety is incorporated within a six-membered ring have been reported [2]. We now describe the synthesis and photochromic properties of 3,4-di(heteroaryl)coumarins. Surprisingly, few routes to 3,4-diarylcoumarins are known; existing procedures are often inefficient and laborious. We have found that the coumarins 3a-f can be obtained *via* acylation of (2-hydroxybenzoyl)heterocycles. Interestingly, 3a undergoes photodehydrocyclisation to the novel pentacycle 4 upon sunlight irradiation, whereas 3b is unreactive. Derivatives of 3c (Ar = 1-naphthyl and 2-naphthyl) are photochromic; the former exists (NMR) as a mixture of atropisomers whereas the latter undergoes rapid conformational interconversion. The synthesis of compounds 3d-f required access to 5; a simple new synthesis of this material has been devised. Attempts to obtain the bis 3-(2,5-dimethyl-3-thienyl)coumarin from 6 gave the alkene 7 stereospecifically. The structure of this compound was established by X-ray crystallography and a mechanism for its formation will be outlined. Extensions of this chemistry will be described.



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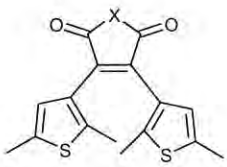
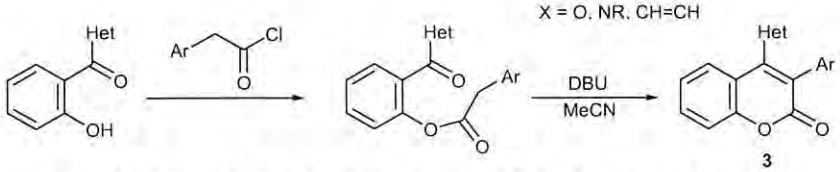


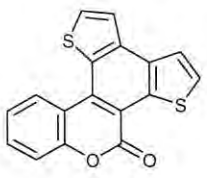
2

X = O, NR, CH=CH



3

a Het = Ar = 2-thienyl; **b** Het = Ar = 3-thienyl; **c** Het = 2,5-dimethyl-3-thienyl, Ar = various;
d Het = Ar = 2,5-dimethyl-3-thienyl; **e** Het = 2,5-dimethyl-3-furyl, Ar = 2,5-dimethyl-3-thienyl
f Het = 5-cyano-1,2-dimethyl-3-pyrrolyl, Ar = 2,5-dimethyl-3-thienyl.



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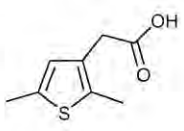

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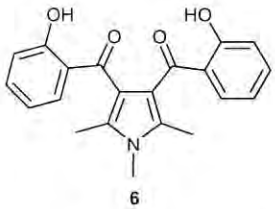

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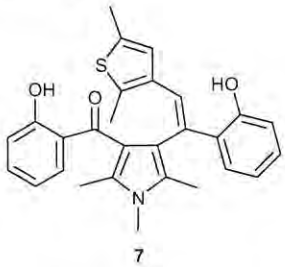

7

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[2] For examples see: Deng X, Libeskind LS, *J. Am. Chem. Soc.* 2001, 123, 7703-7704 (compound 2 X = CH=CH, 1,4-benzoquinones); Yam VW-W, Ko C-C, Zhu N, *J. Am. Chem. Soc.* 2004, 126, 12734-12735 (1,10-phenanthroline); Ivanov SN, Lichitskii B V, Dudinov AA, Martynkin AY, Krayushkin MM, *Chem. Heterocycl. Compd. Engl. Transl.* 2001, 37, 85-90 (1,2,4-triazines)

TP31

LITHIATION AND REDUCTIVE LITHIATION OF CHROMONES – *EN ROUTE* TO FUSED-RING DERIVATIVES

G. Elena Daia, Christopher D. Gabbutt[a], B. Mark Heron[a], John D. Hepworth[a], Janice M. McCreary[a], Simon J. Coles[b] and Michael B. Hursthouse[b]
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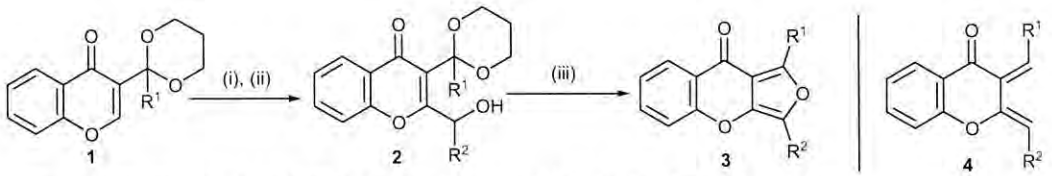
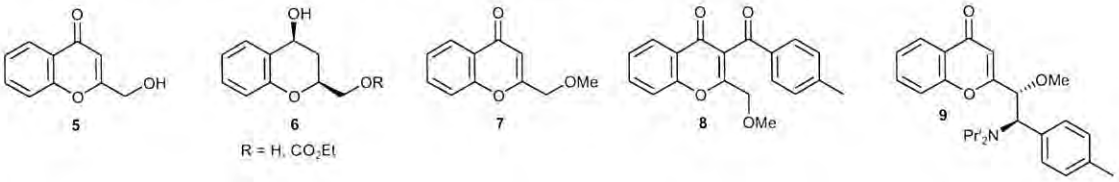
b Department of Chemistry, University of Southampton,Southampton SO17 1BJ, UK

Some time ago we reported [1] that the lithiation of 3-acylchromone acetals 1 followed by electrophilic trapping provided 2-(α-hydroxyalkyl)chromones 2 which can be readily cyclised to the furo[3,4-b][1]benzopyrans 3. The latter represent stable synthetic equivalents of 4.

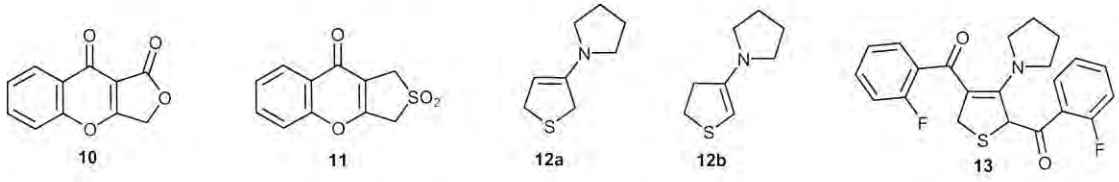


Reagents: (i) LTMP, -78 °C; (ii) R^2CHO; (iii) TsOH, PhMe, Δ R^1 = H or Me; R^2 = Me, Et, 4-MeC_6H_4

We were unable to obtain 3 (R^2 = H) by this approach. We therefore sought to obtain these furans *via* dimetallation of 5. It has now been found that treatment of 5 with lithium 2,2,6,6-tetramethylpiperidide (LTMP) or LDA effects reduction of the chromone ring to give a *cis*-chromanol 6 (R = H). Conducted in the presence of $ClCO_2Et$, the reaction furnishes the ester 6 (R = CO_2Et). Lithiation-electrophilic trapping experiments of the ether 7 follow an entirely different course. Particularly noteworthy are the formation of the acylchromone 8 upon addition of 4-MeC_6H_4COCl together with the stereoselective formation of the β-aminoether 9, the structure of which was established by X-ray crystallography. The mechanisms for these reactions and attempts to generate furobenzopyrans 3 (R^2 = H) will be described.



We have previously employed S_NAr reactions of *ortho*-fluorobenzoyl compounds for the construction of chromones [2]. A tandem *C*-acylation-S_NAr reaction of 2-$FC_6H_4COCH_2CO_2Et$ with $AcOCH_2COCl$ has been investigated as an entry to the furanone 10. In a somewhat related approach to an alternative equivalent of 4, efforts to obtain the thienobenzopyran 11 focussed on the reactions of enamines 12a,b (3:1 a:b) with 2-FC_6H_4COCl, form which 13 has been isolated. Mechanisms will be presented to account for these observations.



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TP32

SHORT SYNTHESIS OF SPIROLACTAMS BY A COMBINATION OF MULTICOMPONENT REACTION AND RADICAL CICLIZATION MICROWAVE ASSISTED.

Maria del Rocío Gámez Montaño[1*], Tannya Rocio Ibarra Rivera[1], Luis Demetrio Miranda Gutiérrez[2*]
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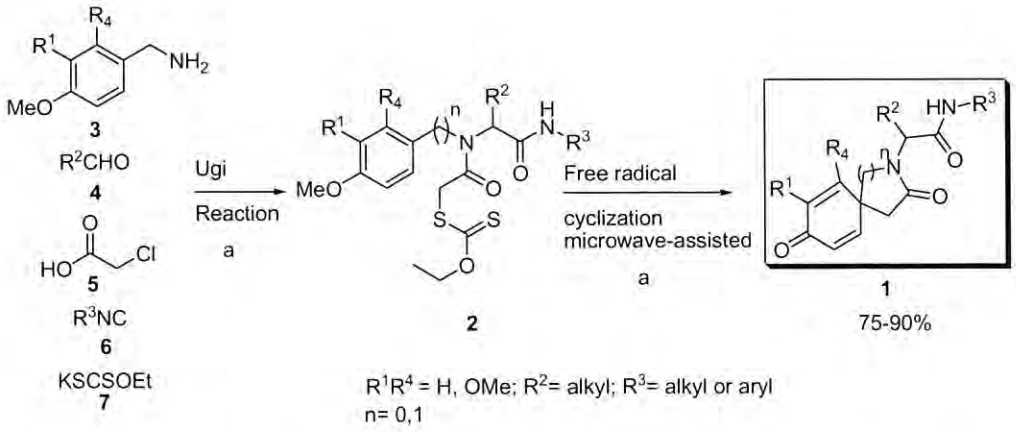
[2]*Instituto de química, Universidad Autónoma de México*

Our interest in the efficient generation of important cyclic nitrogen-containing motifs like azaspirodecanes, has led us to investigate a strategy, witch relies on the sequential use of the Ugi multicomponent reaction with a carbon-carbon bond-forming free radical microwave assisted.

The versatile strategy we now report allows the introduction of the xanthate and aromatic functionalities in a five components Ugi reaction. This allows us to control ring size and periphery features in the products based in the choice of staring materials. As demonstrated in de the scheme 2, the Ugi reactions will generate a substrate containing both the xanthate and the aromatic ring around a central nitrogen core. Subsequent cyclization via free radical reaction will produce the desired N-Scaffold, spirolactam **1** (Scheme 1).

Scheme 1. synthetic route of spirocyclic cyclohexadienones **1**.



The five components Ugi condensation reactions afforded the desired product 2 in excellent yields (90-98%). The xanthates 2 were converted into spirocyclic derivatives 1 in high yields (75-85%) upon exposure to stoichiometric quantities of lauroyl peroxide in toluene and 250 watts less than 25 min.

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TP33

REACTION OF RESORCINOL AND ITS DERIVATIVES WITH 1-(2,2-DIMETHOXYETHYL)-1-METHYL-3-PHENYLUREA — A NEW APPROACH TO THE SYNTHESIS OF IMIDAZOLIDINE-2-ONES

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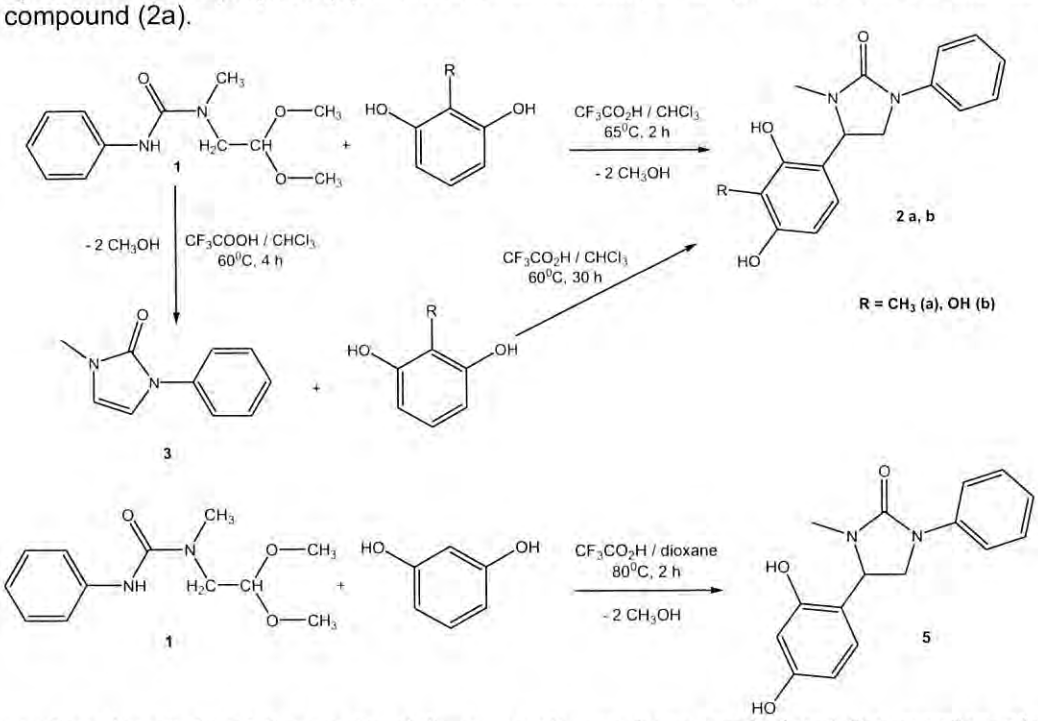
The most common way for the synthesis of calix[4]resorcinols is the condensation of resorcinol and its derivatives with various aldehydes and acetales. We have carried out the reaction of 2-methylresorcinol with 1-(2,2-dimethoxyethyl)-1-methyl-3-phenylurea (1) hoping to obtain corresponding calixarene bearing the urea substituents on the lower "rim" of a molecule. Surprisingly, the product of this reaction was not the expected calixarene, but the heterocyclic compound (2a). The structure of this compound was proved by NMR 1D and 2D. In order to know whether the heterocycle formation is possible in the reaction conditions we carried out the model reaction. It was shown that the product of this reaction is 1-methyl-3-phenyl-1H-imidazol-2(3H)-one (3). Interaction of this compound with 2-methylresorcinol led to the compound (2a).



Expanding the circle of the nucleophilic reagents, we have carried out the reaction of the acetale (1) with resorcinol and pyrogallol. In case of pyrogallol the only product of this reaction was the heterocyclic compound (2b). It was also obtained by the interaction of heterocycle (3) with the pyrogallol. The structure of this compound was confirmed by NMR 1D spectroscopy and x-ray analysis. The interaction of acetale (1) with resorcinol was not so unequivocal and led to the inseparable mixture of products. When the same reaction was carried out in dioxane instead of chloroform, the heterocyclic compound (5) was obtained.

According to the literature data, the synthesis of imidazolidine-2-ones generally is carried out by interaction of diamines with reagents such as phosgene, bis(trichloromethyl)carbonate, diethylcarbonate, di-tert-butylcarbonate and so on. Thus, the interaction of 1-(2,2-dimethoxyethyl)-1-methyl-3-phenylurea (1) and similar compounds with nucleophilic reagents such as phenols seems to be a novel and convenient approach to the synthesis of imidazolidine-2-one derivatives.

Acknowledgement: This work was supported by Russian Foundation for Fundamental Research (grant № 05-03-32136).

TP34

SYNTHEIS OF NOVEL ARYL- AND HETEROARYL-SUBSTITUTED 2(5*H*)-FURANONES AND DIHYDROPYRROL-2-ONES

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Fimbrolides, 3-alkyl-4-bromo-5-(bromomethylene)-2(5*H*)-furanones, isolated from the red marine alga *Delisea pulchra*, have been shown to interfere with the N-acylated homoserine lactone (AHL) mediated cell-cell autoinduction pathways found in many Gram-negative bacteria. As a part of an ongoing project on the structure-function activity of fimbrolides, a range of new aryl- and heteroaryl-substituted furanones have been prepared from the halogenated furanones *via* Suzuki-Miyaura coupling. This coupling reaction has been further extended to form new classes of antagonists, the dihydropyrrol-2-ones and the bicyclic indol-2(4*H*)-ones. These compounds behave as potent antagonists of bacterial signaling pathways present in Gram-negative bacteria. The synthesis and biological activity of these new analogues will be presented.

TP35

ZIP IT UP: A DOUBLE DIELS-ALDER APPROACH TO TETRACYCLES

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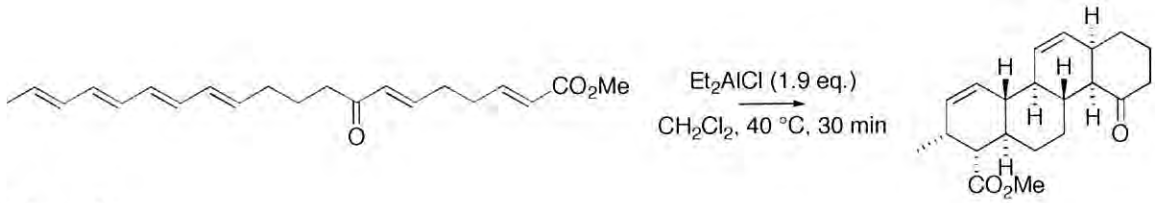
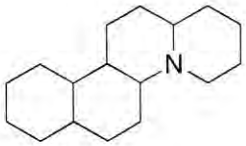
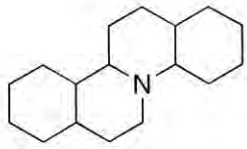
The "zipper-mode" domino intramolecular Diels-Alder sequence is a powerful method to furnish tetracyclic frameworks. In a single step, two discrete cycloadditions transform an acyclic precursor into a complex tetracycle, generating four new sigma bonds and up to eight new stereogenic centres (Scheme 1).[5,6]



Scheme 1

The scope and control of this reaction has been explored and work to date will be presented, with a particular emphasis on the creation of the following **heterocycle**-containing polycyclic frameworks:





References:

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[6] Turner, CI., Williamson, RM., and Sherburn, MS. *Chem. Commun.*, 2003; 1610-1611

TP36

COMPLETELY REGIO- AND STEREOSELECTIVE AZIRIDINE RING OPENING

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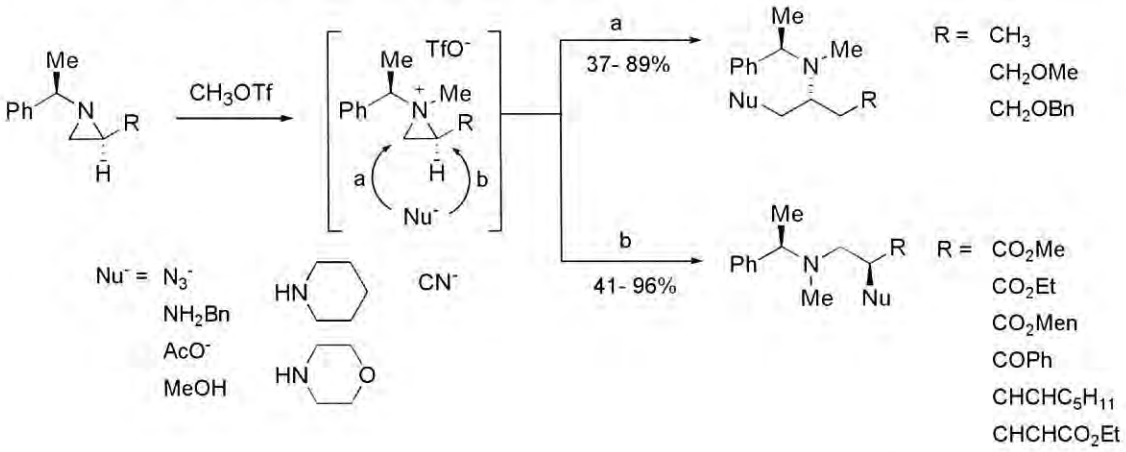
2-Substituted aziridines with an electron donating substituent, α-methylbenzyl, on the nitrogen is quite inert to ring opening reactions toward most nucleophiles. The nitrogen atom should be activated by a suitable electrophile to result an aziridinium ion prior to the nucleophilic attack for the ring opening. Thereby, the applicable nucleophiles are limited to the reagents which can provide an electrophile as its counter part.[1,2]



This limitation can be overcome by methylating the ring nitrogen to make the aziridinium ion by the reaction with methyl trifluoromethanesulfonate which readily reacts with the various external nucleophiles including amine, azide, alkoxide, and cyanide. The ring opening reactions are completely regio- and stereoselective to yield single isomer depending on the substituent at C-2 of the aziridine ring.

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TP37

IODINE-INDUCED REACTION CASCADES TO PREPARE HETEROCYCLIC MOLECULAR SCAFFOLDS

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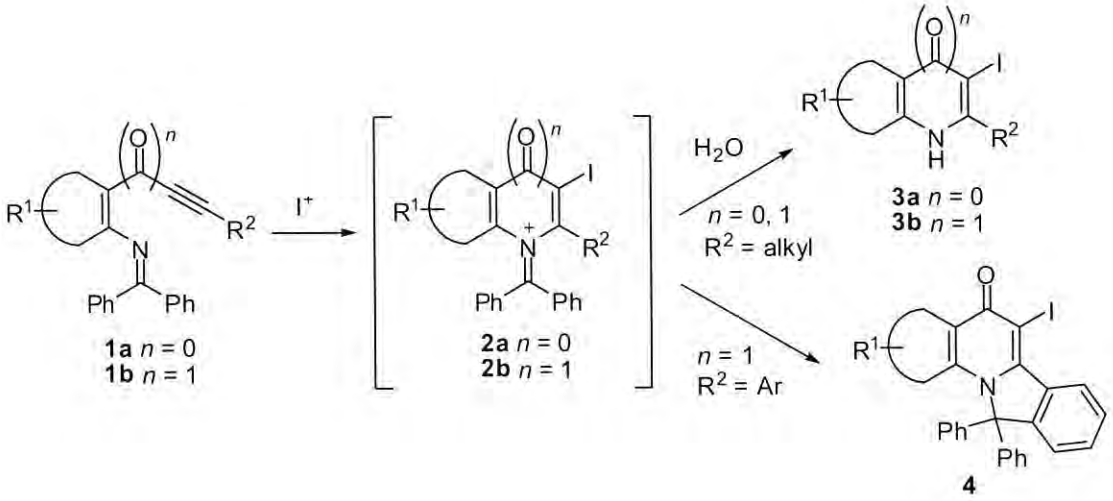
The iodocyclization of various heteroatoms-containing molecules with functionalized alkynes has provided an effective method to prepare a large range of fused-heterocyclic compounds.[1] In our ongoing work in this area, we are extending this chemistry to offer an access to various important heterocyclic scaffolds such as indoles and quinolinones. The current focus is based on the use of a facile protecting group, such as an imine in **1**, to execute the iodocyclization onto an alkynyl unit bearing different functional groups. Depending on the nature of the alkynyl component and the reaction conditions employed, we anticipate two different outcomes whereby when R^2 is an alkyl-bearing substituent and water is presence, the cleavage of the imine group is expected to give quinolinone **3b**. However when R^2 is an aryl substituent and anhydrous reaction condition used, the intermediate **2b** can be "trapped" to give quinolinone **4**. This poster will describe our investigations on the use of different protecting groups and the subsequent iodocyclization result.



Scheme 1. Iodocyclization method based on an imine containing compounds.

References:
1. Hessian KO, Flynn BL. Org. Lett., 2006; 8, 243-246 and references cited therein

TP38

ELECTROCHEMISTRY OF PORPHYRIN-APPENDED DENDRIMERS

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5,10,15,20-Tetrakis(3,5-di-*tert*-butylphenyl) porphyrin was mono-functionalised at the β-pyrrolic position and appended to six generations of porphyrin-appended PAMAM dendrimers. Electrochemical experiments were carried out on the compounds, which showed excellent electrochemical response in solution. These compounds were also able to be immobilised on the electrode surface as a highly stable monolayer, which could be stripped and reformed simply by altering the electrochemical scan potentials.

Stable porphyrin-containing monolayers have a wide potential application as molecular sensors, as they are able to readily undergo redox reactions[1]. Much research has been carried out towards the creation of liquid and gas molecular sensors, wherein a main difficulty is in creating a molecule which will form a surface monolayer which is both stable and generates reproducible signals; characteristics which these monolayers were shown to strongly possess. Porphyrin macrocycles are able to be functionalised with an immense number of different functional groups, as well as being extremely good at binding metals and ligands alike. The architecture of porphyrin-appended PAMAM dendrimers on the electrode surface exhibits possibilities for ligand-based sensors to be appended and the potential for molecular sensing of these compounds is therefore extensive.

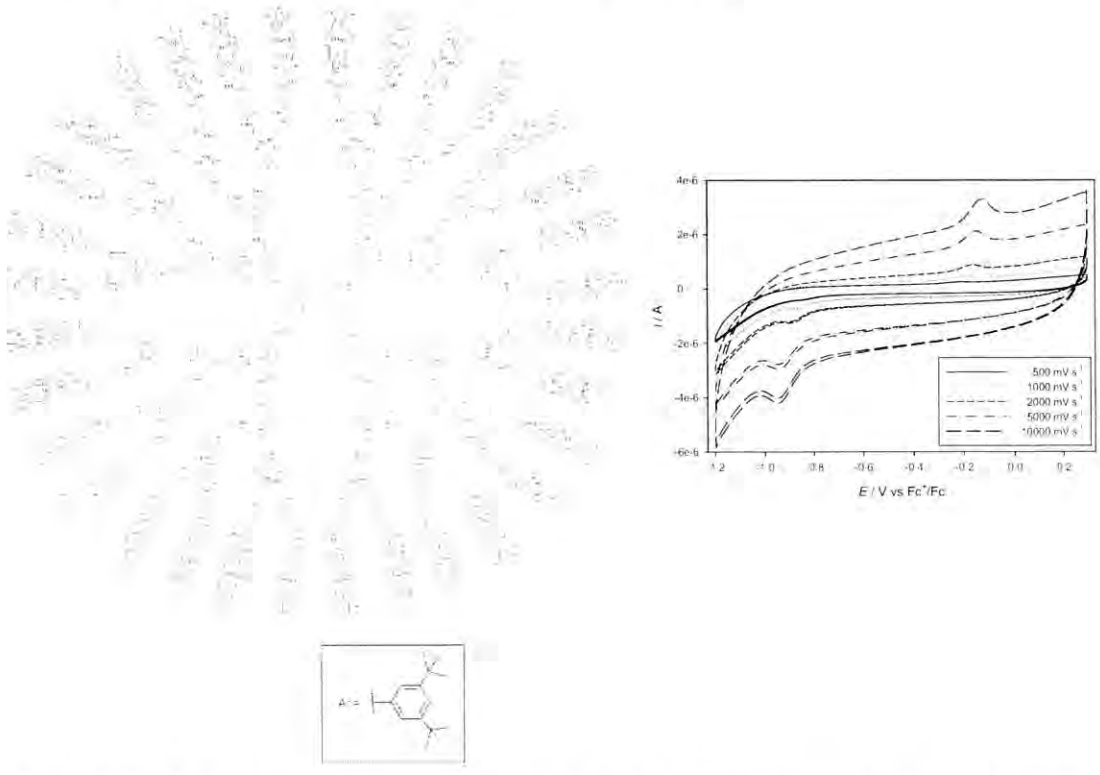

Figure 1. The structure of third generation porphyrin-appended PAMAM dendrimer (left), and its electrochemical response when immobilised on glassy carbon electrode (right).

References:
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TP40

STEREOSELECTIVE OXIDATION OF LITHIUM ENOLATES OF □-AMINOALKANOATES

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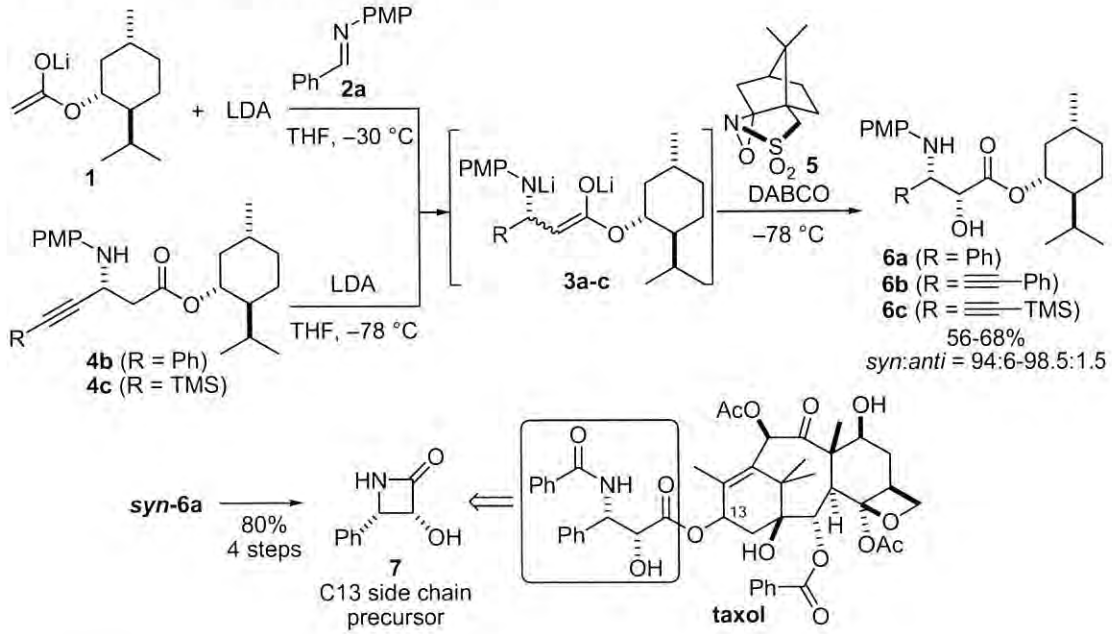
β-Amino-α-hydroxyalkanoates are the fundamentals of biologically active structures. Straightforward construction of this motif is the oxidation of lithium enolate of β-aminoalkanoate. During our studies on asymmetric Mannich reaction of lithium ester enolate we had a chance to study the oxidation of lithium enolate of β-amino alkanoate to give β-amino-α-hydroxyakanoate, which is an intermediate for the key precursor of taxol C13 side chain.

Lithium enolate of *l*-menthyl acetate 1 complexed with LDA reacted with PMP-aldimine 2a to generate dianion 3a. Dianions 3b,c were also generated from β-aminoalkanoate 4b,c. These dianions 3a-c were treated with (–)-camphorylsulfonyloxaziridines 5 to introduce OH group at α position. Especially, the oxidation with 5 in the presence of DABCO gave *syn*-product 6a-c in reasonably high stereoselectivity.



References:

a) Hata S.; Iguchi M.; Iwasawa T.; Yamada K.; Tomioka K. *Org. Lett.*, 2004; 6, 1721-1723.

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d) Fujieda H.; Kanai M.; Kambara T.; Iida A.; Tomioka K. *J. Am. Chem. Soc*, 1997; 117, 2060-2061.

TP41

RING CONTRACTION DURING THE 6π ELECTROCYCLISATION OF NAPHTHOPYRAN VALENCE TAUTOMERS

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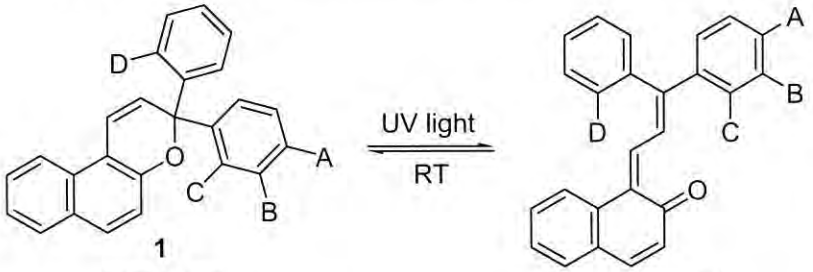
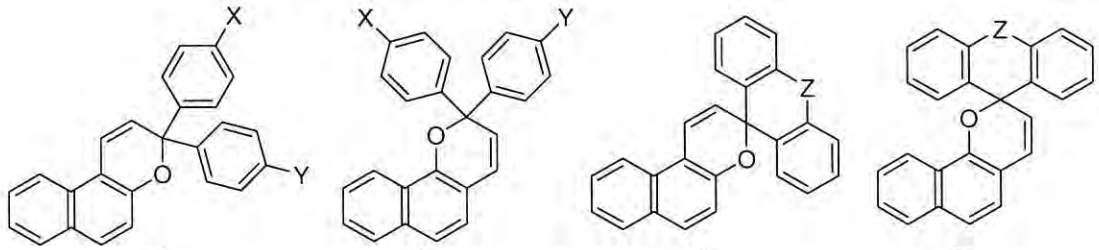
The T-type photochromic response of diarylnaphthopyrans is typically characterised by rapid, intense colour generation with excellent colour persistence and good fatigue properties [1]. We have demonstrated the ability to manipulate the photochromic response of 3,3-diaryl-3*H*-naphtho[2,1-*b*]pyrans *e.g.* 1, through choice and location of substituents (A – D). Thus precise control over colour (λ_{max}) [2] and persistence (rate of fade) [3] has been achieved and even development of complex absorbance bands [4] has been accomplished.



1

colourless coloured

Recently our attention has focussed upon the synthesis and photochromic response of some diarylnaphthopyrans that contain sulfur substituents in one or both of the diaryl rings *e.g.* 2 – 5. In particular, we have explored the oxidation of the sulfur atom to afford sulfones and diastereoisomeric sulfoxides.



2 **3** **4** **5**

X and / or Y selected from H, SMe, S(O)Me, $S(O_2)Me$ Z selected from S, SO and SO_2

The change from sulfur(II) through sulfur(IV) to sulfur(VI) results in a predictable hypsochromic shift in λ_{max} with an increase in the persistence of the developed colour for both series of naphthopyran isomers. Irradiation (365 nm) of solutions of the individual sulfoxide diastereoisomers results in selective conversion, *via* the electrocyclic ring-opening – ring-closing process, into a single, thermodynamically stable diastereoisomer.
Irradiation or heating of solutions of the sulfone 4, X = SO_2, resulted in the rapid loss of photochromism which has been attributed to a ring contraction to afford a naphthofuran. The alternative isomer 5, X = SO_2 requires more extensive irradiation or heating to effect the ring contraction. Full mechanistic discussions supported by spectroscopic data and crystal structures will be presented to account for these observations.

References:
[1] Hepworth JD, Heron BM, in Functional Dyes, ed. Kim S-H, Elsevier (Amsterdam) 2006, p. 85 – 135.
[2] Gabbutt CD, Heron BM, Instone AC, Horton PN, Hursthouse MB, *Tetrahedron*, 2005, 61, 463 – 471.
[3] Gabbutt CD, Heron BM, Instone AC, *Heterocycles*, 2003, 60, 843 – 855.
[4] Gabbutt CD, Heron BM, Instone AC, *Tetrahed*

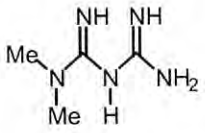
TP42

HYPOGLYCEMIC EFFECTS OF METFORMIN DERIVATIVES IN NORMAL MICE

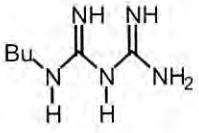
Hajime Kubo, and Kimio Higashiyama

Institute of Medicinal Chemistry, Hoshi University School of Pharmacy and Pharmaceutical Sciences; 2-4-41 Ebara, Shinagawa-ku, Tokyo, 142-8501, Japan

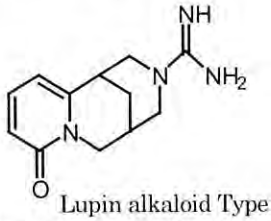
Metformin of the biguanide system hypoglycemic agents is a comparatively simple structure, and the blood sugar level descends by activating the AMPK (5'-AMP activated kinase) and promoting the sugar use in the peripheral organization. As for the promotion of the sugar use in the peripheral organization, the same effect as the movement will be achieved though the action of metformin is not used to treat comparatively weak and alone. Therefore, it is thought that it becomes the hypoglycemic agents of a new type if the compound that can strongly activate AMPK can be discovered.
Then, we pay attention to the biguanidine group that exists in metformin, synthesize the new type compound that has the biguanidine group, and are aiming at the development of the new diabetic medicine.



Metformin

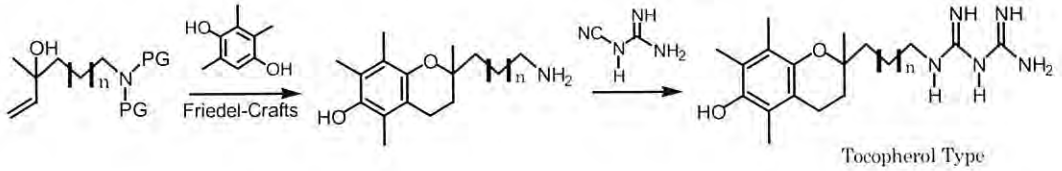


Buformin

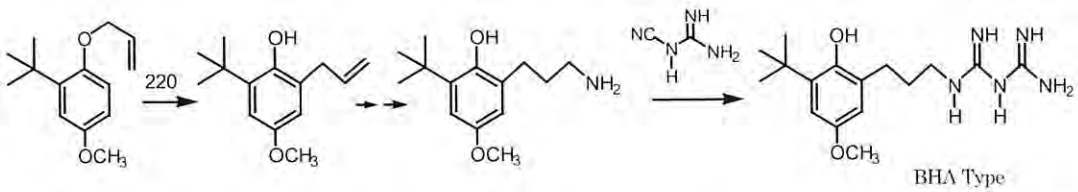


Lupin alkaloid Type

The new type compounds that introduced the guanidine group into the lupin alkaloid that had a weak effect of hypoglycemic had the effect of the same grade as metformin. However, the compound that had strong effect to surpass metformin was not obtained.
On the other hand, the compound that introduced the biguanidine group into the tocopherol derivative or butylated hydroxyanisole derivative (BHA) that had the antioxidative effect showed the hypoglycemic effect that was stronger than metformin. Especially, the compound that united the tocopherol derivative or butylated hydroxyanisole derivative with the biguanidine group in two or three carbon chains showed the hypoglycemic effect that was stronger than metformin.



Tocopherol Type



BHA Type

It is thought that these compounds that can be easily synthesized are lead compounds for the development of a new diabetic medicine.

Reference:
Kubo H. Kobayashi J. Higashiyama K. Kamei J. Fujii Y. and Ohmiya S. *Biol. Pharm. Bull.*, 2000, 23, 114-117; Kubo H. Inoue M. Kamei J. and Higashiyama K. *Biol. Pharm. Bull.*, 2006. 29, 2046-2050.

TP43

SYNTHESIS OF NEW PYRROLO[2,3-D]PYRIMIDINES ANTAGONISM IN EXPERIMENTAL ACUTE PANCREATITIS IN RATS

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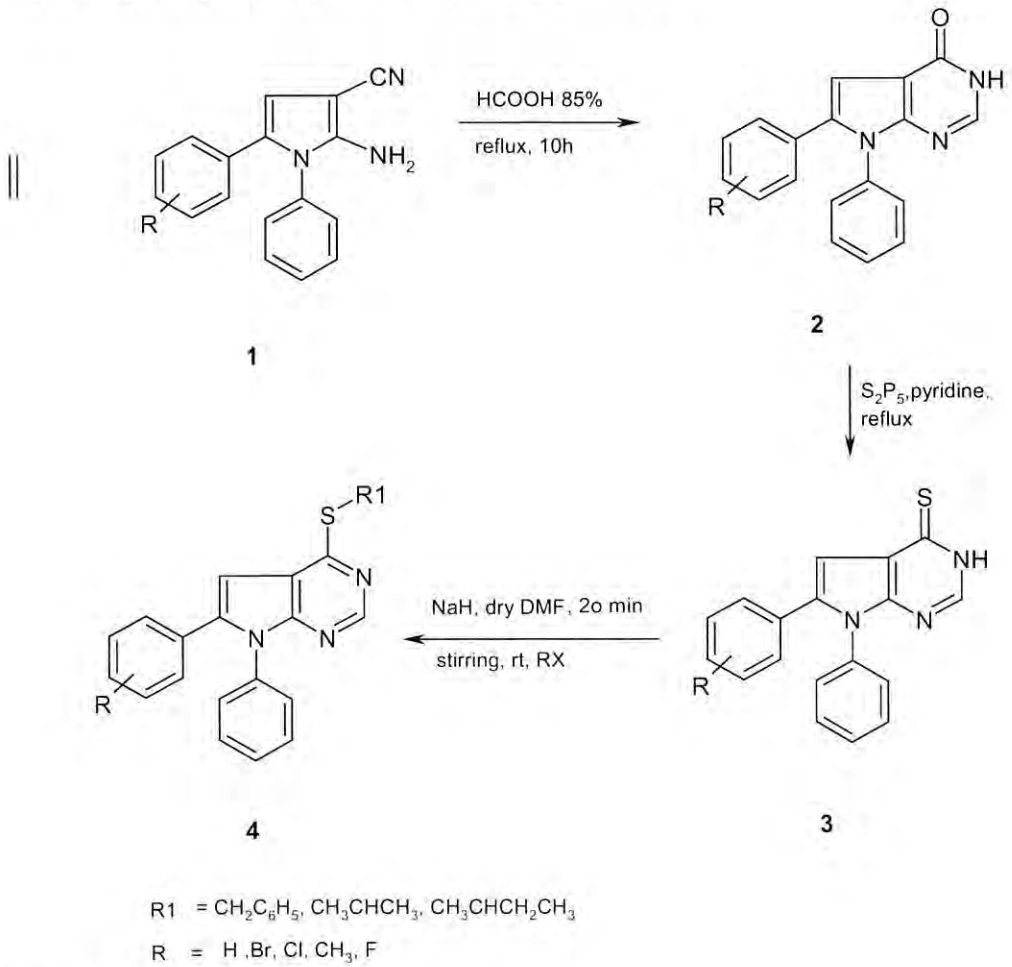
The starting materials 2-amino-3-carbonitrile pyrroles[1] 1 were converted into pyrrolo[2,3-*d*]pyrimidin-4-ones 2, via the reaction with formic acid 85%. Then the latter compounds 2 were reacted with P_2S_5 in presence of dry pyridine and reflux to afford the derivatives of pyrrolo[2,3-*d*]pyrimidin-4-thione 3, which were reacted with alkyl halides(R^1X = 2-bromopropane, 2-bromobutane, benzyl bromide) in dry DMF to give derivatives of 4-alkylsulfanyl-6-aryl-7-phenyl-7*H*-pyrrolo[2,3-*d*]pyrimidine 4.



R1 = $CH_2C_6H_5$, CH_3CHCH_3, $CH_3CHCH_2CH_3$

R = H ,Br, Cl, CH_3, F

References:
1- Hilmy KMH, Pedersen EB, Liebigs Ann.Chem. (1989; 1145-1146).

TP44

MULTIMETAL CATALYSED HYDROALKOXYLATION: A HIGHLY EFFICIENT APPROACH FOR THE SYNTHESIS OF SPIROKETALS

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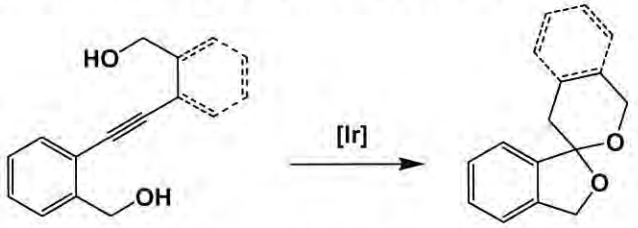
School of Chemistry, University of New South Wales, Sydney, 2052, Australia

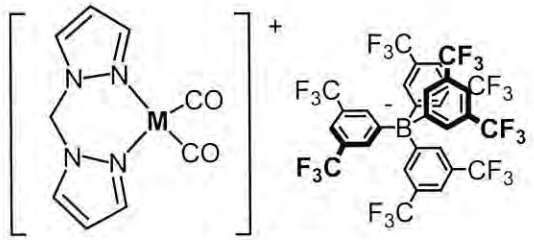
Spiroketals are an important class of heterocyclic molecules because of their occurrence as substructures in a variety of natural products and biologically active compounds. These include HIV protease inhibitors, insect pheromones and pesticides as well as polyether antibiotics.[1,2] Numerous methods are known for the synthesis of these heterocycles. Among these, an attractive and atom-economical route is via the transition metal-catalysed addition of an oxygen nucleophile across the alkyne triple bond (Scheme 1).



Scheme 1

Multimetal catalysts containing two or more metal centres are known to be active catalysts for a variety of single step transformations. Bimetallic complexes can display cooperative effects between the metals, leading to efficiencies which cannot be realised using single catalysts.[3] Bimetallic complexes can also potentially promote two-step synthetic processes, where the individual steps are mechanistically distinct.

Bimetallic catalytic system can be prepared by using bitopic ligands to form the bimetallic complexes. Alternatively, a mixture of two single catalysts can be used to effect the catalysis. Our interest in bimetallic catalytic systems of the group 9 metals led us to investigate the use of mixtures of Rh/Ir catalysts (**1** and **2**) for the double hydroalkoxylation of alkynes.



1 (M = Rh)
2 (M = Ir)

References:
(1) Ghosh, A. K., Leshchenko, S., Noetzel, M., J. *Org. Chem.* 2004, 69, 7822.
(2) Schwartz, B. D., Hayes, P. Y., Kitching, W., De Voss, J. J., J. *Org. Chem.* 2005, 70, 3054.
(3) Broussard, M. E., Juma, B.; Train, S. G., Peng, W-J., Laneman, S. A., Stanley, G. G. *Science* 1993, *260*, 1784-1788.

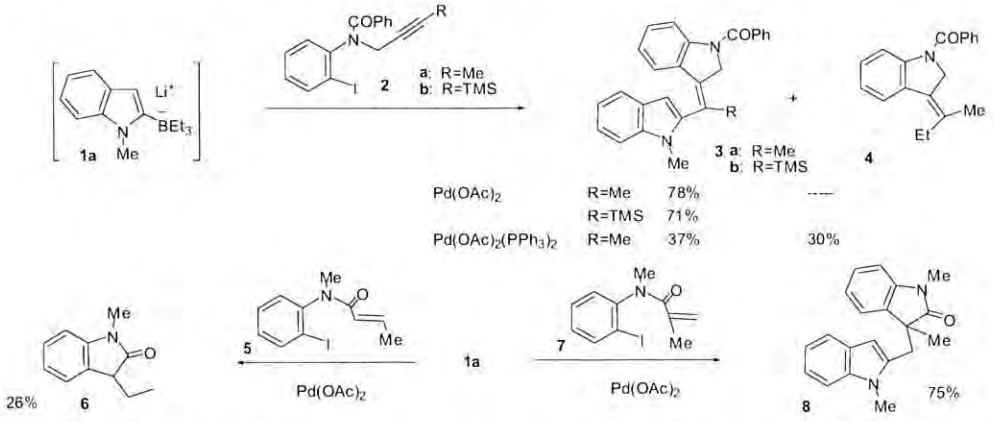
TP46

INDOLYLBORATE AS A BUILDING BLOCK FOR INDOLE ALKALOIDS

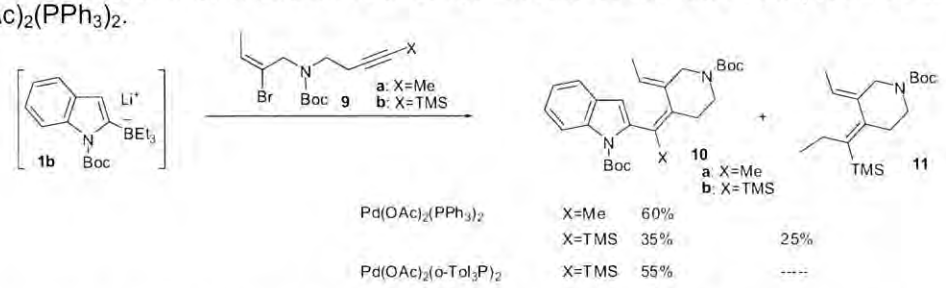
Norinobu Takahashi, Minoru Ishikura, and Koji Yamada

Faculty of Pharmaceutical Sciences, Health Sciences University of Hokkaido

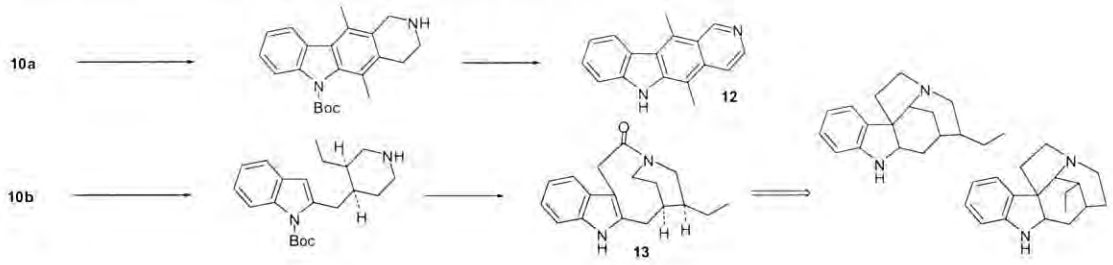
Suzuki cross-coupling protocol has now emerged as the method of choice in various chemical transformations, whereas the use of organoboron compounds for the tandem cross-coupling process is limited significance [notably, tetravalent organoboron compound (borate complex) has proven to offer less practical advantages]. We have previously disclosed indolylborate (1) is highly effective in the cross-coupling process. By taking advantages of the attractive features of 1, we have interested in the use of 1 as a transfer agent in the tandem cross-coupling process and the synthetic use of it for indole alkaloids.
Treatment of 1a with 2 smoothly proceeded to give 3 in good yield, whereas marked retardation of the yield of 3a along with substantial amounts of 4 was observed depending on the catalyst used. Treatment of 1a with 5 was messy, resulting in the isolation of 6. Otherwise, 1a smoothly reacted with 7 to produce 8.



The coupling reaction of 1b could also be effected with 9, providing 10. Substantial amounts of 11 was observed when the reaction of 1b with 9b was carried out in the presence of $Pd(OAc)_2(PPh_3)_2$.



Preparation of ellipticine (12) was effected through photo-cylization of 10a. Catalytic hydrogenation of 10b and the subsequent cyclization step allowed the formation of 13. Conversion of 13 to indole alkaloids is in progress.



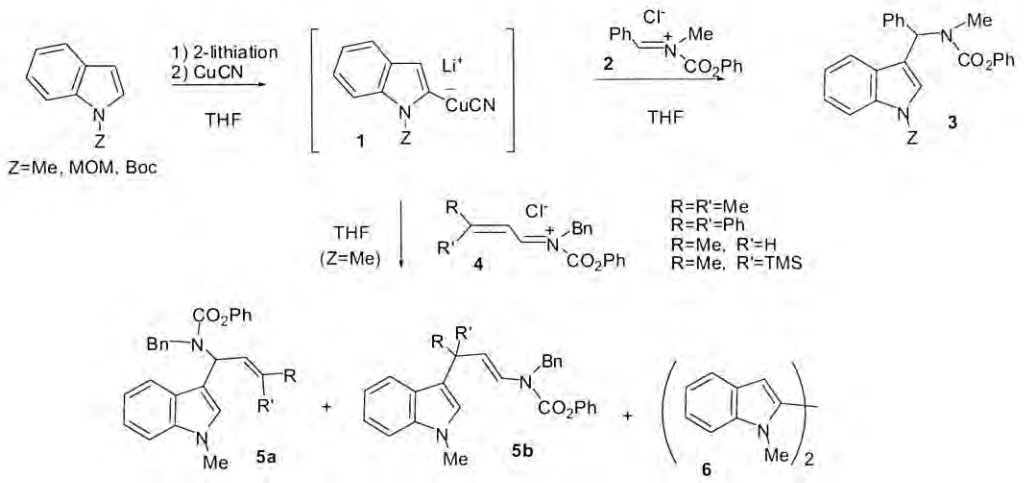
TP47

INVESTIGATION OF THE REACTION OF INDOLYLCYANOCUPRATES WITH IMINIUM SALTS

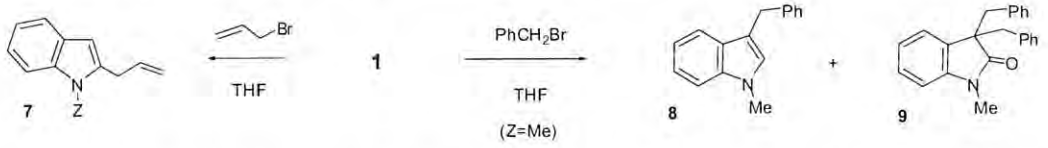
Hiroyuki Komatsu, Minoru Ishikura, and Koji Yamada

Faculty of Pharmaceutical Sciences, Health Sciences University of Hokkaido

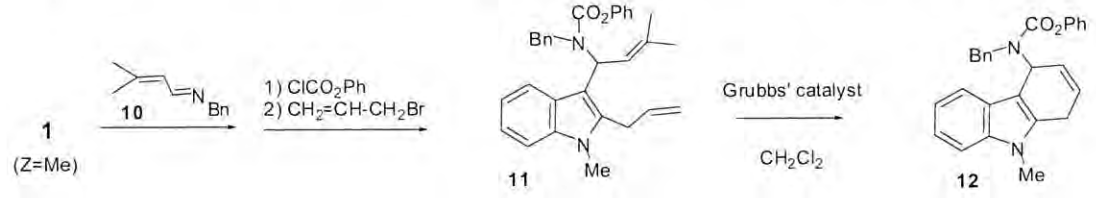
Organocopper reargents have been routinely used in organic synthesis. During our investigation devoted to the development of a new synthetic method based on organometallic reagents, indolylcuprates (1), generated from the corresponding indoles *in situ*, was found to react with iminium salt (2) to give 3-substituted indoles (3) in a highly regioselective manner. The reaction of 1 (Z=Me) with ene-iminium salt (4) also proceeded to allow the isolation of a pair of 3-substituted indoles (5a and 5b) and a small amount of dimer (6).



Treatment of 1 with allyl bromide regioselectively led to 2-allylindoles (7), whereas subjection of benzyl bromide to the reaction with 1 (Z=Me) under the same conditions allowed the isolation of 3-benzylindole (8) along with oxindole (9), though in low yields.



Furthermore, we simply undertook the reaction as follws; To a THF solution of 1 and ene-imine (10) in the presence of amine as a proton scavenger, $ClCO_2Ph$ was added. After 15min allyl bromide was added, and then the mixture was gradually warmed to room temperature, allowing the formation of 11 in a one-pot protocol. Subsequent subjection of 11 to metathesis reaction in the presence of Grubbs' catalyst afforded carbazole 12. Further investigation of the present reaction directed toward the preparation of indole alkaloid is in progress.



TP48

SYNTHESIS AND CYTOTOXIC ACTIVITY OF 3-ALKYLIDENE-5-ARYLDIHYDROFURAN-2(3H)-ONES

Anna Janecka,[a] Jakub Fichna,[a] Anna Albrecht,[b] Marek Rozalski,[c] Urszula Krajewska,[c] Kazimierz Studzian[a] and Tomasz Janecki[b]

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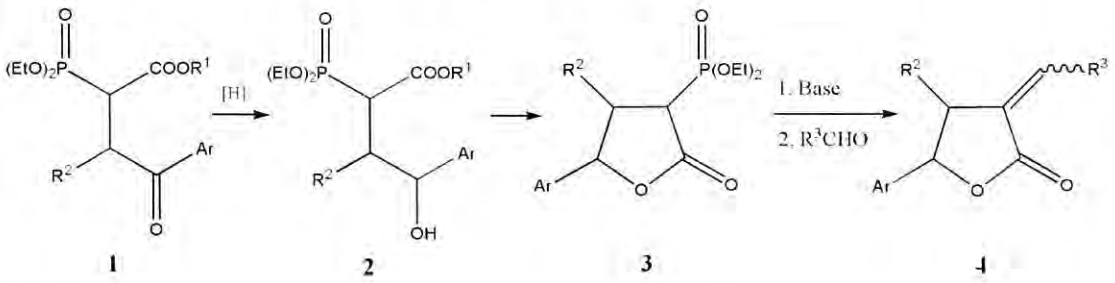
α-Alkylidene-γ-lactone framework can be found in many natural compounds exhibiting a wide spectrum of biological activities such as cytotoxic, antimicrobial or antifungal [1].
In our search for highly cytotoxic, yet structurally simple α-alkylidene-γ-lactones as possible drug candidates [2] we synthesized a series of 3-alkylidene-5-aryldihydrofuran-2(3H)-ones 4, applying the reaction sequence shown on the Scheme.



Scheme

Readily available 4-aryl-2-diethoxyphosphoryl-4-oxobutanoates 1 were reduced to 4-aryl-2-diethoxyphosphoryl-4-hydroxybutanoates 2, which lactonized giving 5-aryl-3-diethoxyphosphoryltetrahydrofuran-2-ones 3. Horner-Wadsworth-Emmons olefination of 3, using various aldehydes, yielded dihydrofuran-2(3H)-ones 4.
Cytotoxicity of compounds 4 was tested against several leukemia cell lines (L-1210, HL-60, NALM-6). Several dihydrofuran-2(3H)-ones 4 were found to be very potent.

References:
[1] Hoffman, H. M. R., Rabe, J. Angew. *Chem.*, Int Ed. Engl. 1985; 24, 94.
[2] Albrecht A., Kedzia J., Koszuk J. F., Warzycha E., Janecki T. Tetrahedron Lett., 2006; 47, 2353-2355; Janecki T., Wasek T., Rozalski M., Krajewska U., Studzian K., Janecka A. Bioorg. Med. Chem. Lett., 2006; 16, 1430-1433; Janecki T., Blaszczyk E., Studzian K., Janecka A., Krajewska U., Rozalski M. J. Med. Chem., 2005; 48, 3516-3521.

TP49

INVESTIGATIONS INTO 2-AMINOQUINOLINE DERIVATIVES AS LIGANDS FOR THE TEC SH3 DOMAIN

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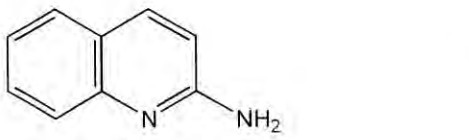
[2]*School of Molecular and Biosciences, University of Adelaide, Adelaide, Australia*

The SH3 domain is found in a wide variety of proteins that are involved in a large number of cellular signalling pathways.[1,2] Many of these pathways, when deregulated lead to diseases such as cancer and osteoporosis and are therefore considered valuable targets for the development of therapeutic agents.[3] We have reported that 2-aminoquinoline 1 binds to the Tec-SH3 domain with a K_d of 120 μM and through exploring substitution at the 6-position, have improved the binding of this lead compound by 6 fold.[4,5] Our most recent investigations have involved further exploration of substituents at the 6-position in addition to developing new protein-ligand interactions by substitution at the 3-position. In the 6-position ligands with the structure 2 have been prepared by substitution of a 6-bromomethylquinoline with a variety of phenols under basic conditions. In the 3-position we have investigated substituted phenethyl derivatives, 3 as well as the unsaturated styryl derivative 4. These are prepared through Wittig or Horner-Emmons reactions with a 3-formylquinoline. Recent studies have shown that these substituted 2-aminoquinolines have potential to bind to the SH3 domain with higher affinity with one of each of the 6- and 3-substituted compounds displaying affinity approximately equivalent to our strongest binding ligand to date (K_d = 25 μM). It is expected that further exploration will lead to even higher affinity ligands.



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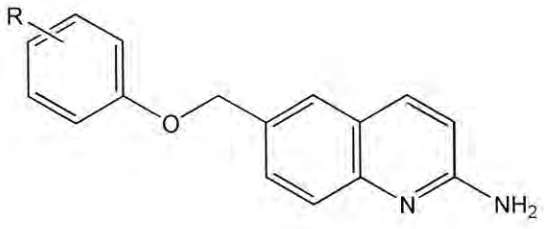

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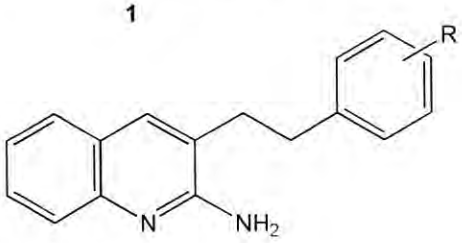

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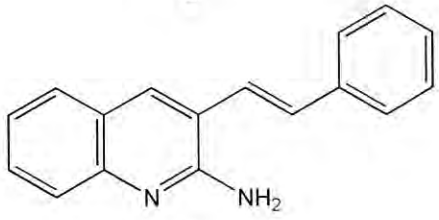

4

(1) Ren, R.; Mayer, B. J.; Cicchetti, P.; Baltimore, D. *Science* 1993; 259, 1157-1161.
(2) Dalgarno, D. C.; Botfield, M. C.; Rickles, R. J. *Biopolymers* 1997; 43, 383-400.
(3) Vidal, M.; Gigoux, V.; Garbay, C. *Crit. Rev. Oncol. Hematol.* 2001; 40, 175-186.
(4) Inglis, S. R.; Stojkoski, C.; Branson, K. M.; Cawthray, J. F.; Daniel Fritz; Wiadrowski, E.; Pyke, S. M.; Booker, G. W. *J. Med. Chem.* 2004; 47, 5405 - 5417.
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TP50

SYNTHETIC STUDIES TOWARDS THE RUBROMYCINS

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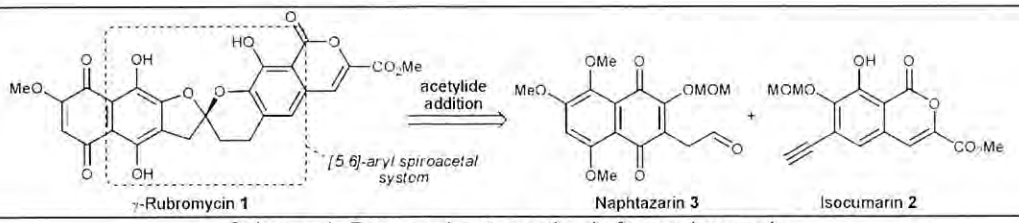
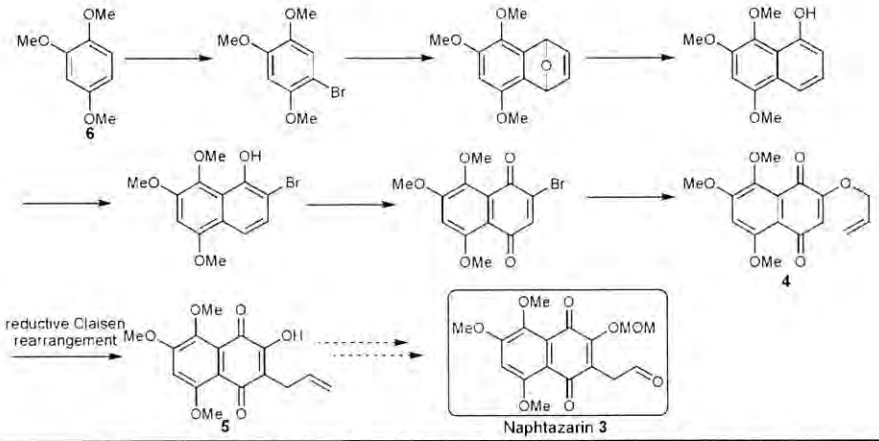
γ-Rubromycin 1 belongs to a unique class of quinone antibiotics isolated from cultures of *Streptomyces sp.*[1] that inhibit human telomerase.[2] Elevated telomerase levels are found in almost all human cancers and frequently correlate with disease progression and the metastatic state.[3] The novel [5,6]-aryl spiroacetal ring system present in the rubromycins is reported to be the essential structural feature responsible for the observed telomerase inhibition.[3,4] This study focuses on the total synthesis of γ -rubromycin 1 building on our previous model work developed to construct [5,6]-aryl spiroacetal analogues of this naturally occurring antibiotic.[5] The key disconnection involves addition of the acetylide derived from isocoumarin 2 to the aldehyde functionality of naphthazarin 3 (Scheme 1). The synthetic route to the naphthazarin moiety 3 of γ-rubromycin focuses on a Claisen rearrangement of allyl ether 4 to allylnaphthol 5. Allyl ether 4 in turn is synthesized from trimethoxybenzene 6 in 6 steps (Scheme 2).



Scheme 1. Proposed retrosynthesis for γ-rubromycin



Scheme 2. Synthesis of naphthazarin required for γ-rubromycin

References:
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2. Ueno, T., Takahashi, H., Oda, M., Mizunuma, M., Yokoyama, A., Goto, Y., Mizushina, Y., Sakaguchi, K. and Hayashi, H. *Biochemistry*, 2000, *39*, 5995.
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TP51

HETEROCYCLIC SYNTHESIS USING MICHAEL ADDITION OF FORMAMIDES TO NITROALKENES FOLLOWED BY 1,3-DIPOLAR NITRILE OXIDE CYCLOADDITION REACTION

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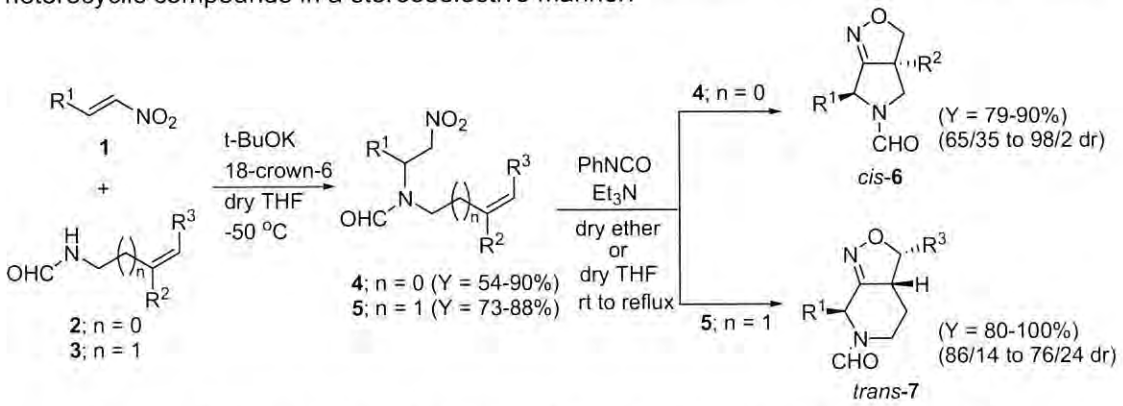
1,3-Dipolar cycloaddition of nitrile oxide is regarded one of a useful synthetic methods in organic synthesis. Through the reaction, γ-amino alcohols or β-hydroxy ketones are readily prepared. Nitroalkenes have been known as good Michael acceptors or dienophiles in the Diels-Alder reaction. Use of nitrogen nuclepohiles often provides a useful precursors for vicinal diamines but β-nitro amines, the adducts of the Michael addition, are usually too labile to use further synthetic work. Amide-nitrogen is also regarded as good nucleophiles but so far only limited examples of Michael addition of amides have been known. Recently we have found formamides act as good nucleophiles in the Michael addition to nitroalkenes to give β-nitroamides in good yield. In this paper we will present the detail of the addition reaction and its application to heterocyclic synthesis.

Treatment of secondary *N*-allylformamides 2 or *N*-homoallylformamides 3 with nitroalkenes 1 in the presence of potassium *tert*-butoxide and 18-crown-6 at -50 ^{0}C in THF resulted in the efficient formation of β-nitroamides 4 or 5 in good yields. These amides were stable enough for the further transformation. Subsequent intramolecular nitrile oxide cycloaddition (INOC) reaction was carried out by treatment of 4 and 5 under standard Mukaiyama conditions, and pyrroloisoxazoles 6 and piperidinoisoxazoles 7 were obtained in good yields. The cycloaddition took place in a stereoselective manner and one of the stereoisomer was formed in around 8:2 to 9:1 selectivity. The diastereomeric ratios of 6 and 7 were determined by GC analyses after removal of the formyl group, which causes rotational isomers making NMR very complicated. The relative configurations of 6 and 7 were determined by their X-ray crystallographic analyses. It should be noteworthy that stereochemistry between C3a and C6 in the major isomer 6 was found to be *cis*, while that between C3a and C7 in the major isomer of 7 was found to be *trans*. Thus, the adducts 6 and 7 were regarded as good precursors for heterocyclic syntheses, and the present method provides a useful access to a variety of aza-heterocyclic compounds in a stereoselective manner.



Scheme 1. The Michael addition of *N*-formamides to nitroalkenes and subsequent INOC reaction.

1) Kamimura, A.; Kadowaki, A.; Nagata, Y. Uno, H. *Tetrahedron Lett.* 2006, *47*, 2471-2473.
2) Kadowaki, A.; Nagata, Y; Uno, H.; Kamimura, A. *Tetrahedron Lett.* 2007, *48*, 1823-1825.

TP52

ENANTIOSELECTIVE SYNTHESIS OF AZA-BAYLIS-HILLMAN ADDUCTS AND THEIR USE FOR HETEROCYCLIC SYNTEHSIS

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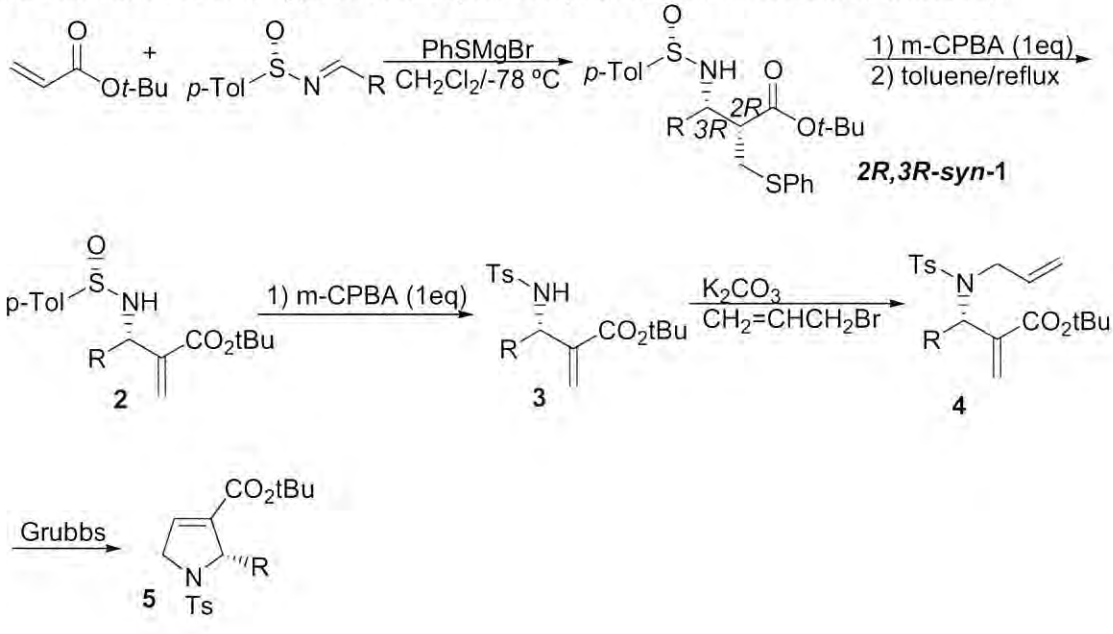
[+]Integrated Center for Sciences, Ehime University, Matsuyama 790-8577,Japan

The Morita-Baylis-Hillman reaction is recognized as a useful reaction in organic synthesis because it provides a one step preparation of β-hydroxy-α-methylene carbonyl compounds from aldehydes and α,β-unsaturated carbonyl compounds. Use of imines instead of aldehydes, which is called the aza-Baylis-Hillman reaction (ABH reaction) gives β-amino-α-methylene esters that serve as a precursor of β-lactams or heterocyclic compounds. Due to utility of the reaction, asymmetric modification of ABH reactions has been explored so far. Recently we have succeeded to develop a new stereoselective ABH equivalent reaction in which chiral sulfinimines are employed as the imine source. Our modification, which contained two-step procedure, Michael/aldol tandem reaction followed by thermal elimination of sulfinic acid, enabled to prepared chiral ABH adducts from aliphatic imines. In this paper we report a new heterocyclic synthesis from chiral ABH adducts.
The stereoselective Michael/aldol reaction was performed as the following way: *tert*-butyl acrylate and chiral sulfinimine was added to a solution of magnesium thiolate in CH_2Cl_2. The reaction proceeded smoothly and the tandem adduct 1 was isolated in high yields. The adduct 1 usually contained a pair of stereoisomers. Stereochemical investigation for 1 revealed that the difference of the stereochemistry came from the difference of configuration at C2 so that the both isomers had the same *R* configuration at C3, the carbon attaching the amino group. Treatment of 1 with 1 equivalent of *m*-CPBA converted 1 into corresponding sulfoxide, which underwent thermal elimination of sulfinic acid to give chiral ABH adduct 2 without significant epimerization. So these two step procedure provide a useful method to prepare chiral ABH adduct with high enantiomeric excesses.
We next examined to convert the chiral ABH adducts to nitrogen heterocyclic compounds. For example, treatment of 1 eqiuivalent of *m*-CPBA, 2 smoothly gave corresponding suflone amide 3, which was ready alkylated at nitrogen by basic treatment. Allylated 4 acted as a efficient precursor of 2,5-dihydropyrrole 5 through RCM reaction catalysed by the 2nd generation of Grubbs catalyst. Throughout the transformation, no significant racemization was observed and highly optically active 2,5-dihydropyrroles were prepared in good yields. The transformation to other type of heterocyclic compounds from 1 will be also discussed.



TP54

DESIGN, SYNTHESIS AND ANALYSIS OF A MINOR GROOVE BINDER PYRROLEPOLYAMIDE NUCLEOSIDE HYBRIDES

Etsuko Kawashima, Yusuke Ohba, Yusuke Terui, Kazuo Kamaike

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Organic compounds capable of controlling gene expression may potentially be used as viable gene therapy agents. In this regard, one of the most important requirements that the medicine must possess is the ability to clearly distinguish target sequences from all other sequences within the genome. Incidentally, it was reported that pyrrolepolyamide molecules such as distamycin A and netropsin[1] which binds to the DNA minor groove can interfere with gene expression by the sequence-specific recognition of DNA.[2] On the basis of this background, we expected that nucleoside bearing a minor groove binder pyrrolepolyamide would be able to regulate gene expression. Therefore we designed and synthesized nucleosides linked to pyrrolepolyamide such as the pyrrolepolyamide-adenosine (Hybrid 1) and -2'-deoxyguanosine hybrids (Hybrid 2, Hybrid 3 and Hybrid 4) as lead compounds for the potential gene therapy agents. The pyrrolepolyamide frame of Hybrid 2, Hybrid 3 and Hybrid 4 combines at the 2-exocyclic amino group of the 2'-deoxyguanosine by a linker and the 2-exocyclic amino group of guanine exists in the minor groove side of duplex. Hybrid 2 is the 2'-deoxyguanosine-pyrrolepolyamide hybrid using the 3-aminopropionyl linker, Hybrid 3 is using the 3-aminopropyl linker and Hybrid 4 is changed the formyl group at the tip of the pyrrolepolyamide of Hybrid 3 to the 1-methylpyrrole-2-carbonyl group (Fig.1).
In this presentation, we report the synthesis and the effect of these compounds for DNA duplex which is clarified from the analytical data of the *Tm* values and the CD spectra.

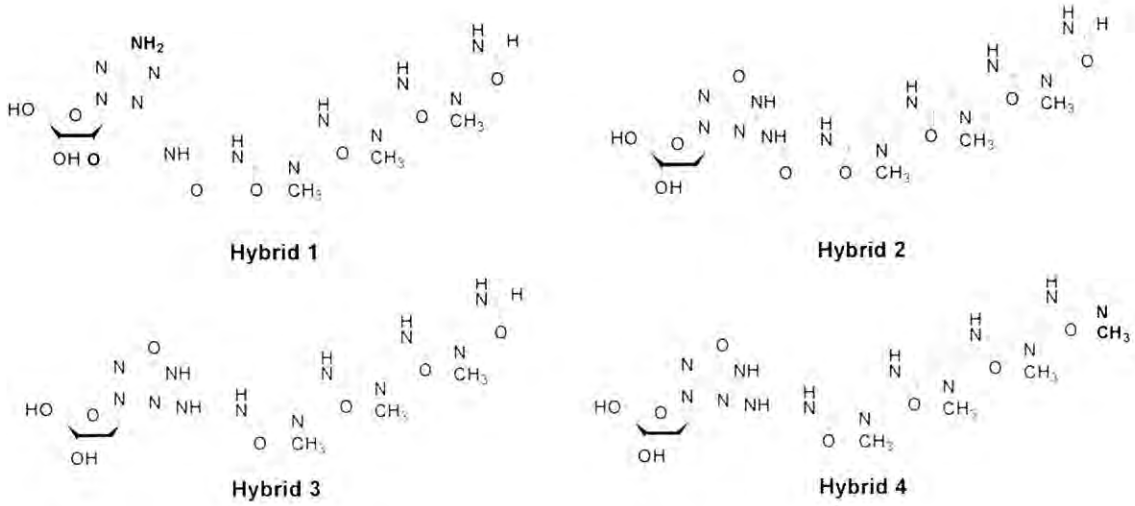

Fig. 1

References:
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TP55

REACTIONS OF THE NIITROGEN HETEROCYCLIC COMPOUNDS WITH UNSATURATED ORGANOPHOSPHORUS DERIVATIVES.

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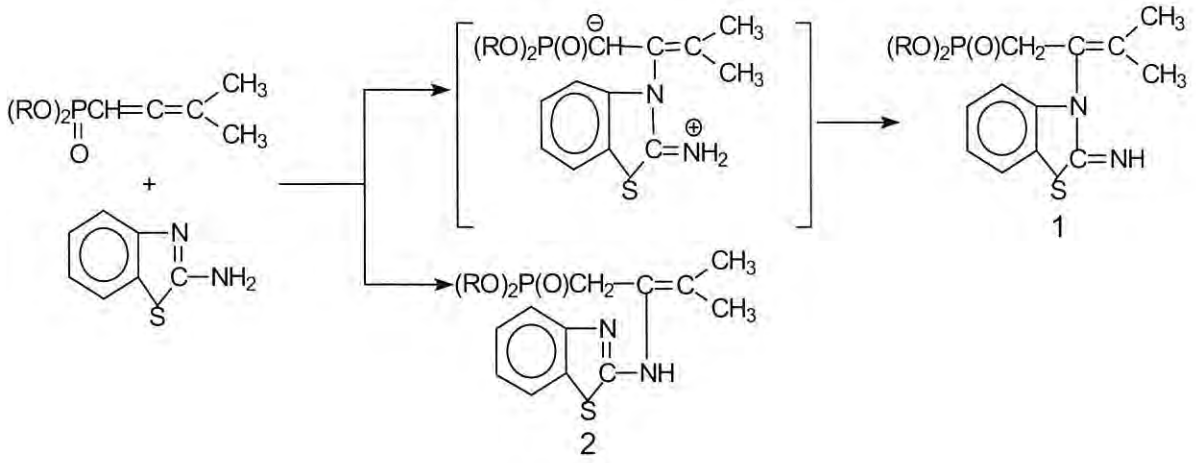
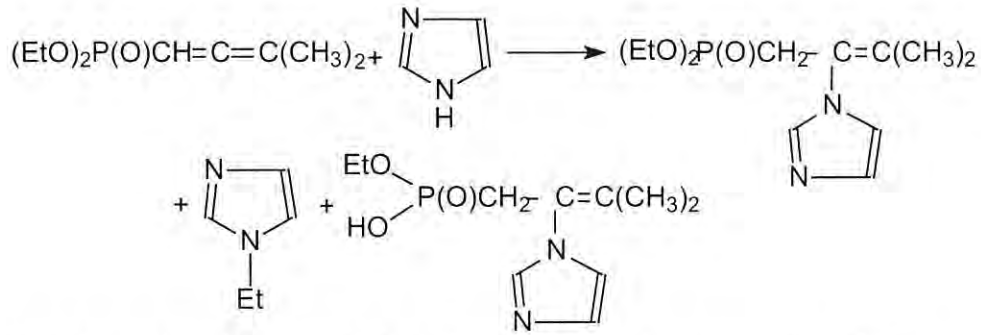
The introduction of different functionalic groups into heterocyclic compounds plays an important role in the modification of them biological activity. We investigated the reaction of 2-aminobenzothiazole with 3-methylbuta-1,2-dienylphosphonates. For this reaction, two pathways are possible: the central C atom of the allene system could be attacked by the ring N-atom (adduct 1) or the N atom of the exocyclic amino group (adduct 2).



The molecular and crystal structures of adduct of reaction of 2-aminobenzothiazole with diethyl 3-methyl-buta-1,2-dienylphosphonates were determined by X-ray diffraction analyses. Thus, the reaction of thiazole with butadienylphosphonate involves the endocyclic N atom of heterocyclic compound and the 1,2-double bond of phosphonate (adduct 1). The resulting adduct 1 cocrystalllizes with the starting aminobenzothiazole,

We have found that the reaction of imidazole with diethyl 3- methylbuta-1,2-dienylphosphonate or diethyl vinylphosphonate proceeds with the formation on a mixture of products:



The introduction of isopropyl- or butyl- groups at the phosphorus atom of allenyl- or vinylphosphonates leads to the absence of N-alkylation of the imidazol cycle.

TP56

DEVELOPMENT OF ROUTES TO DESIGNER TRIAZOLE LIGANDS AND THEIR IRON(II) COMPLEXES

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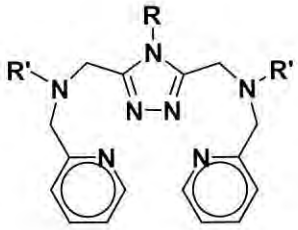
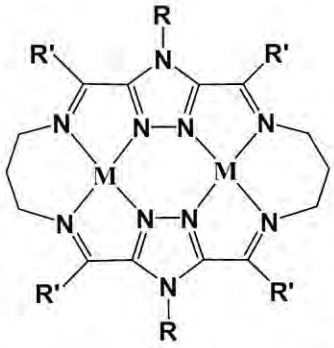
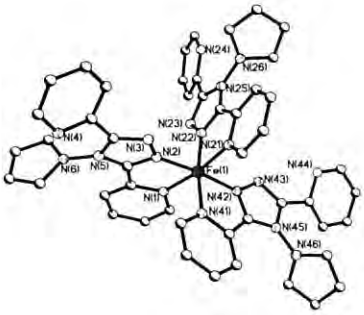
[b] *School of Chemistry, Building 23, Monash University, Clayton, Victoria 3800, Australia.*

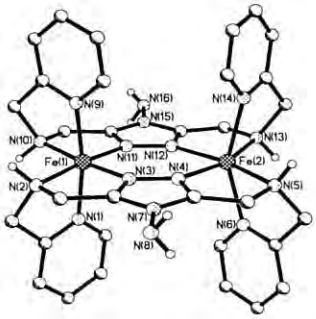
The use of the 1,2,4-triazole moiety in iron(II) spin crossover (SCO) systems has been well documented.[1] The adjacent N^1, N^2 donor atoms in such ligand systems allow for a communication pathway to be established between two or more metal centres. Preparing suitable triazole based ligands is non-trivial but we have prepared a range of ligands featuring a 1,2,4-triazole moiety, with differing N^4 substituents and comprising either bis-bidentate, bis-terdentate or macrocyclic binding pockets which can facilitate the formation of dinuclear triazole-bridged complexes. The synthesis of such ligands will be focused on and a brief overview of the complexation chemistry given focusing primarily on the magnetically interesting metal iron(II).

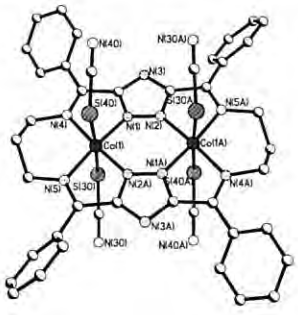




Two state switching, between high spin [HS] and low spin [LS] states, as temperature is varied, has been observed in many mononuclear iron(II) complexes. In contrast dinuclear iron(II) complexes may exhibit switching between three states, [LS–LS], [HS–HS] and also a "[LS–HS]" half SCO form. A variety of mononuclear and dinuclear iron(II) complexes, featuring either bis-bidentate or bis-terdentate triazole ligands, will be presented and discussed.







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Haasnoot, J. G. '1,2,4-Triazoles as ligands for iron(II) high spin-low spin crossovers', ed. O. Kahn, Kluwer Academic Publishers, 1996; Kahn, O. and Codjovi, E. *Phil. Trans. R. Soc. A*, 1996, 354, 359; van Koningsbruggen, P. J., Maeda, Y. and Oshio, H., *Top. Curr. Chem.*, 2004, 233, 259.