TP57

SYNTHETIC STUDY OF NORZOANTHAMINE: SYNTHESIS OF THE ABC RING MOIETY

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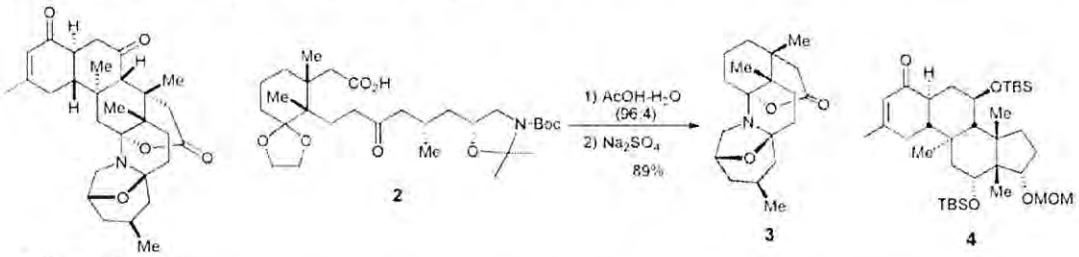
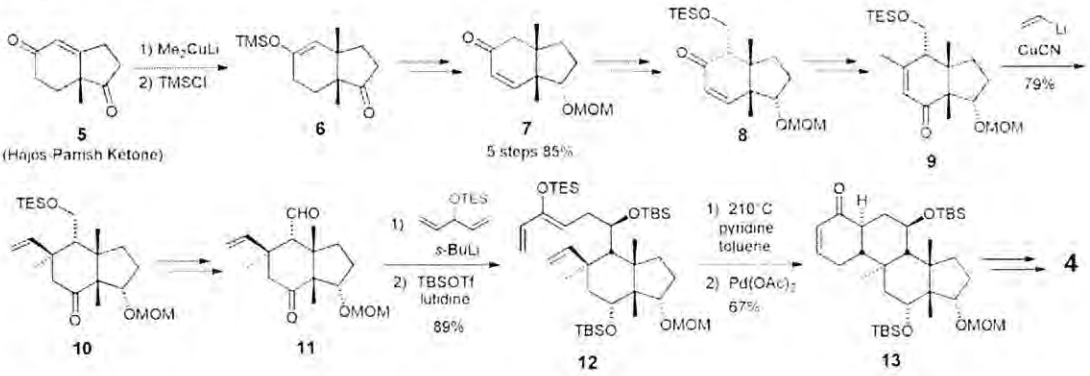
Norzoanthamine[1] (1), discovered by Uemura in 1995, has attracted a great deal of attention from both pharmacological and synthetic points of view. First total synthesis was achieved by Miyashita and Tanino group in 2004.[2] It has been well recognized that there are two major problems to be solved for the total synthesis of norzoanthamine; (1) construction of heterocyclic bisaminal moiety (DEFG ring moiety) which is the most characteristic part of 1, and (2) construction of efficient and stereochemical control in the C ring which contains 4 quaternary chiral carbons. In this context, we have been investigating the synthetic study of norzoanthamine, and we previously developed an efficient methodology for the construction of pentacyclic bis aminal 3 by treating 2 with AcOH-H_2O.[3] This protocol was successfully applied for the total synthesis of 1 by Miyashita and Tanino.[2]



1 Norzoanthamine

During our continuing efforts toward a total synthesis of norzoanthamine, we recently succeeded a synthesis of ABC ring moiety 4. Considering a stereochemically dense C ring, our strategy was to construct a C ring, followed by an intramolecular Diels-Alder reaction furnishing a requisite AB ring. Thus, the quaternary methyl at C22 was selectively introduced by Me_2CuLi addition to Hajos-Parrish ketone (5). Stereocontrol at C12 was found most difficult in the present approach. After a number of unsuccessful attempts, vinyl lithium underwent a stereoselective 1,4-addition to 9 in the presence of CuCN affording 10. Diene unit was installed by Oppolzer's method in high yield. Diels-Alder reaction of 11 proceeded in a stereoselective manner, and the resulting silyl enolether was subjected to a Saegusa-Ito oxidation to obtain enone 13 in 67% yield. ABC ring moiety 4 was successfully synthesized from 13 by conventional method (Me_2CuLi, LHMDS-TMSCl, $Pd(OAc)_2$-O_2) in 62% yield. Manipulation of cyclopentanol moiety in 4 toward a total synthesis of norzoanthamine is under investigation.



References:
1) Fukuzawa, S.; Hayashi, Y.; Uemura, D.; Nagatsu, A.; Yamada, K.; Ijuin, Y., *Heterocyclic Commun.*, 1995, *1*, 207-214.
2) Miyashita, M.; Sasaki, M.; Hattori, I.; Sakai, M.; Tanino, K. *Science*, 2004, *305*, 495-499.
3) Hikage, N.; Furukawa, H.; Takao, K.; Kobayashi, S. *Tetrahedron Lett.*, **1998**, *39*, 6237-6240, 6241-6244. *Idem*, *Chem. Pharm. Bull.*, **2000**, *48*, 1370-1372.

TP58

HETEROPOLY ACID ADSORBED ON SILICA GEL CATALYZED PAAL-KNORR PYRROLE SYNTHESIS UNDER SOLVENT-FREE CONDITIONS

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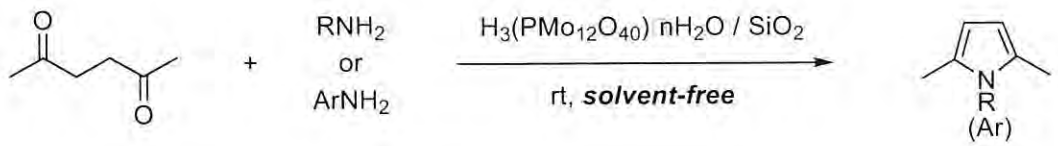
Pyrrole is an important class of heterocyclic compounds in organic, bioorganic, and medicinal chemistry. One of the most common methods to prepare pyrroles is the use of Paal-Knorr synthesis via the condensation of 1,4-diketones with primary amines in the presence of acid catalysts. Although this method can be carried out under mild conditions, there is still some difficulty with acid-sensitive substrates and in separating the products from the catalyst mixture. Therefore, a new system that is simple, clean, efficient, and environment-friendly is highly desirable.

As one promising approach toward this end, we were particularly interested in the use of heteropoly acids due to their advantageous nature of strong acidity, low in toxicity, and moisture- and air-stability. After several experiments, we found that the use of heteropoly acids adsorbed on silica gel under solvent-free conditions could serve as an efficient catalytic system for providing the desired Paal-Knorr pyrrole synthesis.

For example, direct exposure of 2,5-hexanedione and primary aliphatic or aromatic amines to 10 mol% of phosphomolybdic acid on silica gel (910 mg per 1 mmol of amine) at room temperature, the desired pyrroles were obtained in almost quantitative yields. The general scope of this chemistry will be reported.



TP62

MICROWAVE ASSISTED PARALLEL SYNTHESIS OF DIKETOPIPERAZINES: tert-BUTYLISOCYANIDE AS A CONVERTIBLE ISOCYANIDE IN POST-UGI MODIFICATIONS

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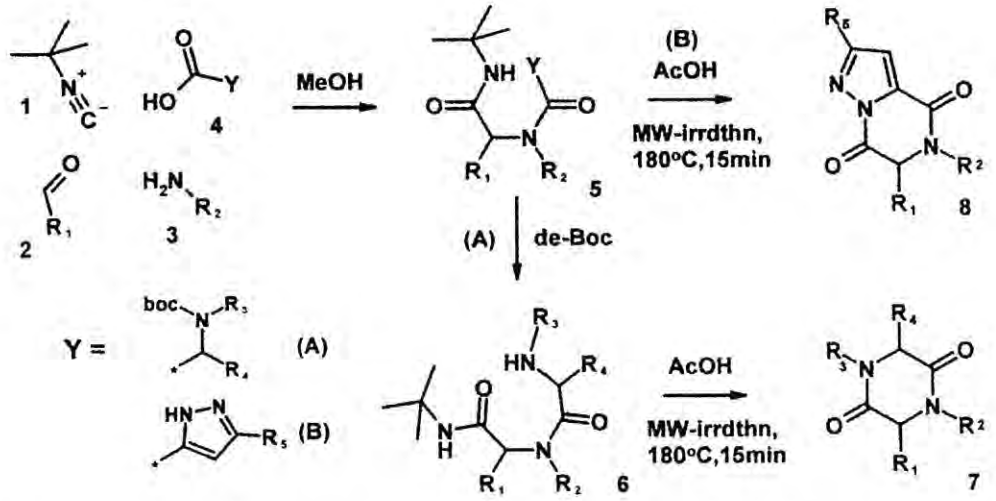
A number of new synthetic approaches have been developed recently to extend utility of Ugi-multicomponent reaction to access a diversity of new heterocyclic systems in simple one-pot manner via post-modification of Ugi-product. One of such approaches is based on convertible isocyanides. The reactivity of newly formed in course of Ugi reaction convertible amide moiety provides possibility for successive reactions with other N-nucleophiles usually via intramolecular attack. Several convertible isocyanides have been developed so far. However, they are either expensive or not available commercially at all. The synthesis of such reagents requires not only considerable efforts but also special handling technique due to the low storage stability of such reagents.
Here we report a new microwave assisted synthetic approach that utilizes a readily available tert-butylisocyanide 1 as convertible isonitrile for post-Ugi modifications. The synthesis of 2,5-diketopiperazine derivatives 7 including their fused analogues 8 was accomplished in the manner that is presented on the Scheme.



The protection-de-protection strategy was employed for the synthesis of substituted 2,5-diketopiperazines 7 starting from Boc-protected (un)natural amino-acids 4(A). Dipeptides 6 obtained after Boc-cleavage of primary Ugi-adducts 5(A) were heated under microwave irradiation for 15 min at 180°C providing the target compounds 7 with 50-90% overall yield. Similar approach was proposed earlier [1] for the diketopiperazine core synthesis based on unstable Armstrong's convertible isocyanide.
The same conditions were used for the synthesis of 8 via cyclization of primary Ugi adducts 5(B) obtained from pyrazole-carboxylic acids 4(B).
In both cases, a multi-step synthetic sequence was accomplished in one-pot parallel synthesis manner with simple work-up procedure.

References:
[1] Hulme, C.; Morrissete, M.M.; Volz, F.A.; Burns, C. *Tetrahedron Lett,* 1998, 39, 1113-1116.

TP63

NEW TRIAZOLOPYRROLOPYRAZINE SYSTEMS BY 1,3-DIPOLAR CYCLOADDITION

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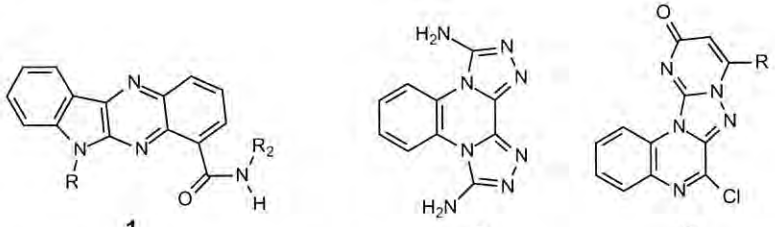
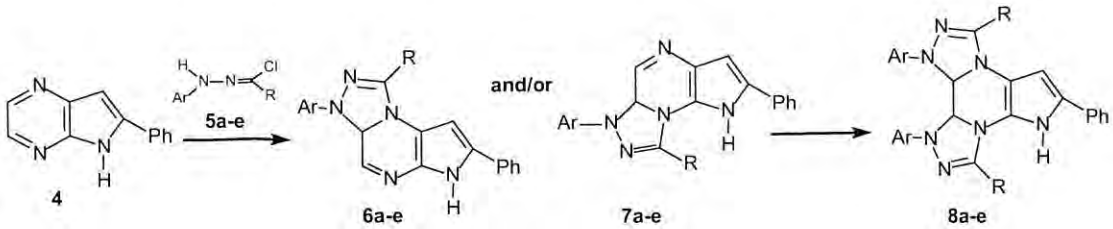
A large number of compounds containing pyrrolopyrazine and triazolopyrazine moieties showed marked activity in many biological systems. Indolo[2,3-b]quinoxalines of type 1 represent an important series of DNA intercalating agents endowed with antiviral and cytotoxic activities [1-3]; the triazoloquinoxaline derivatives of type 2 and 3 show antibacterial activities [4].



1 2 3

In our hand the synthesis of new triazolopyrrolopyrazine ring systems, with potential biological activities, occurs by 1,3-dipolar cycloaddition reactions. The addition, highly *regio* and *sito*-selective [5], of dipole nitrilimines, generated *in situ* from the corresponding chloroarylhydrazones 5a-e, to 2-phenylpyrrolopyrazine ring, allows the construction of new triazolopyrrolopyrazine systems of type 8a-e in one pot. In the course of the reaction it was possible to isolate, as well, the tricyclic precursor systems 6a-e, 7a-e.



a: R=COOMe, Ar=Ph; b: R=COPh; Ar=Ph; c: R=COOEt; Ar=pCl-Ph;
d: R=COMe; Ar=Ph; e: R=Ar=Ph.

Mechanicistic aspects of the cycloaddition reactions and the stereochemistry of the products will be discussed.
The antiproliferative activity of all the derivatives of the new ring systems is currently under investigation.

References:
[1] Harmenberg J, Aakesson-Johansson A, Graeslund A, Malmfors T, Bergman J, Wahren B, Aakerfeldt S, Lundblad L, Cox S *Antiviral Res.*, 1991, 15, 193-203.
[2] Harmenberg J, Wahren B, Bergman J, Akerfeldt S, Lundblad L, *Antimicrob. Agent Chemother.*, 1988, 32, 1720-1724.
[3] Skarin T, Rozell BL, Bergman J, Toftagard R, Moller L, *Chem. Biol. Interactions*, 1999, 122, 89-106.
[4] Nasr M, Nasr A, *Arch. Pharm. Med. Chem.*, 2002, 8, 389-394.
[5] a) Aversa MC, Bonaccorsi P, Giannetto P, *J. Heterocycl. Chem.*, 1989, 26, 1619-1622. b) Grubert L, Patzel M, Jugelt W, Riemer B, Liebscher J, *Liebigs Ann. Chem.*, 1994, 1005-1011. c) Grubert L, Jugelt W, Breb J, Koppel H, Strietzel U, Dombrowski A, *Liebigs Ann. Chem.*, 1992, 885-894.

TP64

SYNTHESIS AND PHOTOINDUCED ELECTRON TRANSFER IN β,β'-PYRROLIC FUSED FERROCENE-PORPHYRIN-FULLERENE TRIADS

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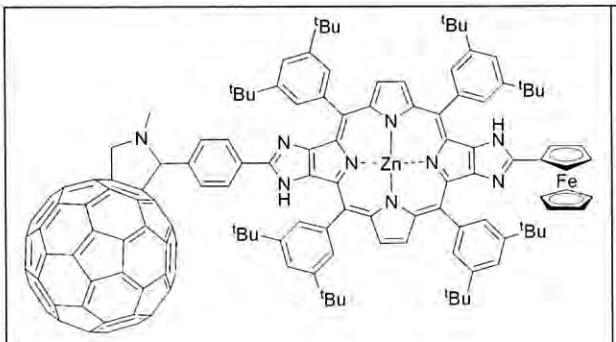
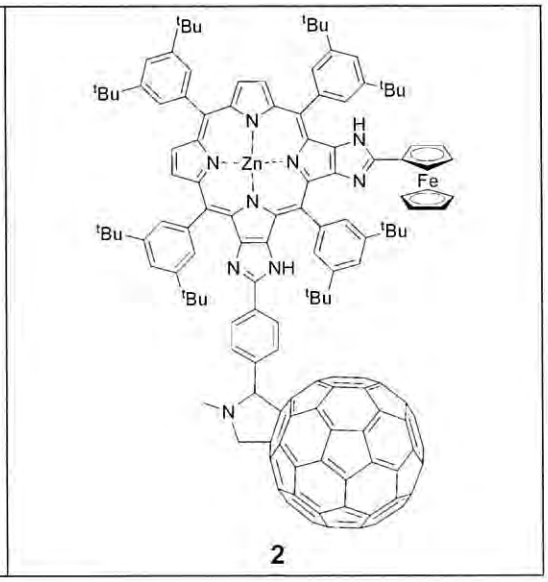
Mimicry of the natural photosynthetic reaction centre has been a very active research area in recent years due to the possibility of achieving improved efficiencies in solar energy conversion devices. The high efficiency of the natural system is due to the multi-step electron sequence. Donor-bridge-acceptor triads are the most common approach in the mimicking of the multi-step electron transfer sequence.[1]
Porphyrins are often used in artificial photosynthetic system as they are similar to the natural chromophores. The incorporation of fullerene as an electron-acceptor is widespread because of its symmetrical shape, large size and π-electron system. The resulting small reorganization energy required for electron transfer slows down the charge recombination rate in porphyrin-fullerene dyads.[2]
Previously, our group has synthesized and studied a linear β,β'-pyrrolic fused ferrocene-(zinc porphyrin)-fullerene (Fc-ZnP-C_{60}) 1.[3] This triad affords the final charge-separated lifetime of 630 μs which is the longest ever reported in the similar triads. Here we describe the synthesis and investigate the photophysical properties of a non-linear Fc-ZnP-C_{60} 2. We will discuss the resulting directionality effects in communication through porphyrin rings where communications with ferrocene and fullerene enhance the forward electron transfer rate within the molecule and slow down the recombination of the final charge-separated state.





References:
1. a. Gust D, Moore TA, and Moore AL, *Acc. Chem. Res.*, 2001; 34, 40-48.
   b. Imahori H, Tamaki K, Araki Y, Sekiguchi Y, Ito O, Sakata Y, and Fukuzumi S, *J. Am. Chem. Soc*, 2002; 124, 5165-5174.
2. Imahori H, Tkachenko NV, Vehmanen V, Tamaki K, Lemmetyinen H, Sakata Y and Fukuzumi S, *J. Phys. Chem. A*, 2001; 105, 1750-1756.
3. Curiel D, Ohkubo K, Reimers J, Fukuzumi S, and Crossley MJ, *Phys. Chem. Chem. Phys.*, 2007; submitted.

TP66

SYNTHESIS OF SIMPLE ARYL SPIROKETALS RELATED TO THE TELOMERASE INHIBITOR γ-RUBROMYCIN

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The rubromycins are a family of quinone antibiotics isolated from a strain of *Streptomyces* species that exhibit activity against Gram-positive bacteria.[1,2] γ-Rubromycin (Figure 1) contains a 5,6-spiroketal moiety which in turn is linked to a hydroxynaphthoquinone chromophore and an isocoumarin moiety,[3] and it is postulated that the spiroketal moiety is in fact the important pharmacophore for the observed inhibition of human telomerase.[1] To date, the synthesis of simple 5,6-bisbenzannelated[4] and 6,6-bisbenzannelated[5] spiroketals related to γ-rubromycin have been reported. We herein report the synthesis of a series of 6,6-bisbenzannelated spiroketals that contain additional oxygen atoms, namely the 3*H*,3'*H*-2,2'-spirobi[benzo[*b*][1,4]dioxine] ring system (Figure 2). These novel heterocyclic scaffolds related to γ-rubromycin can be used to probe the effect that introduction of additional heteroatoms might have on telomerase inhibition and DNA binding.

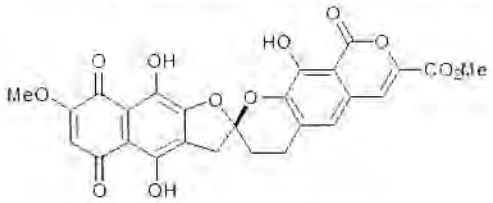

Figure 1 Structure of γ-rubromycin

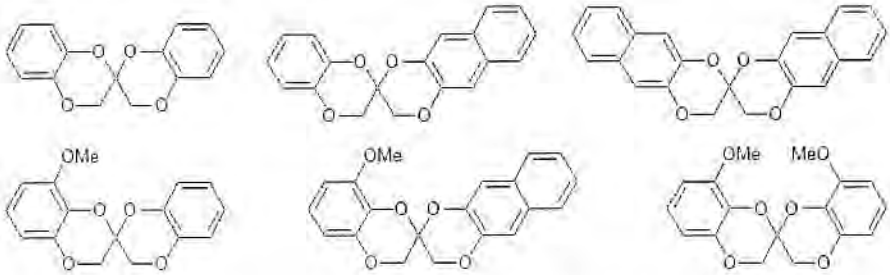

Figure 2. Novel aryl spirodioxines based on a 3*H*,3'*H*-2,2'-spirobi[benzo[*b*][1,4]dioxine]

References:

[1] Ueno, T, Takahashi, H, Oda, M, Mizunuma, M, Yokoyama, A, Goto, Y, Mizushina, Y, Sakaguchi, K, Hayashi, H. *Biochemistry*, 2000; 39, 5995–6002.

[2] (a) Brockmann, H, Lenk, W, Schwantje, G, Zeeck, A. *Tetrahedron Lett.*, 1966; 7, 3525–3530; (b) Brockmann, H, Lenk, W, Schwantje, G, Zeeck, A. *Chem. Ber.*, 1969; 102, 126–151; (c) Brockmann, H, Zeeck, A. *Chem. Ber.*, 1970; 103, 1709–1726.

[3] Bringmann, G, Kraus, J, Schmitt, U, Puder, C, Zeeck, A. *Eur. J. Org. Chem.*, 2000; 2729–2734.

[4] (a) Capecchi, T, de Koning, CB, Michael, JP. *Tetrahedron Lett.*, 1998; 39, 5429–5432; (b) Capecchi, T, de Koning, CB, Michael, JP. *J. Chem. Soc., Perkin Trans. 1*, 2000; 2681–2688; (c) Siu, T, Qin, D, Danishefsky, SJ. *Angew. Chem. Int. Ed.*, 2001; 40, 4713–4716; (d) Zhou, G, Zheng, D, Da, S, Xie, Z, Li, Y. *Tetrahedron Lett.*, 2006; 47, 3349–3352; (e) Lindsey, CC, Wu, KL, Pettus, TRR. *Org. Lett.*, 2006; 8, 2365–2367; (f) Tsang, KY, Brimble, MA, Bremner, JB. *Org. Lett.*, 2003; 5, 4425–4427.

[5] Brimble, MA, Flowers, CL, Trzoss, M, Tsang, KY. *Tetrahedron*, 2006; 62, 5883–5896.

TP67

SYNTHESIS OF PHENYLENE-VINYLENE-THIENYLENES OLIGOMERS WITH AND WITHOUT CYANO SUBSTITUENTS AND THE STUDY OF THEIR PHOTOPHYSICAL PROPERTIES

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The synthesis of new oligo(phenylene-vinylene) (OPV) derivatives has attracted considerable attention due to their widespread application in light-emitting diodes, chemical sensors, nonlinear optics, organic magnetic materials, and flat-panel displays. However, to date, the corresponding development of organic materials for red electroluminescence lags significantly behind that for the other two primary colors (green and blue). Therefore, there still remains much room for improvement on the materials for red OLED. Our preliminary results from ZINDO calculations on our previous PPV type oligomers and with thiophene ring to replace the phenylene moieties showed that thiophene ring could cause large red shifts in the absorption spectra. The presence of the alkoxy unit should enhance the solubility of oligomers and the introduction of high electron affinity of cyano groups on the vinylene linkages of OPV derivatives has been reported to lower the energy of the LUMO and reduces the barrier to the electron injection in LED. Thus, PPV derivatives containing cyano groups on the vinylene linkage present high electron affinity and therefore exhibit a relatively low threshold voltage and high quantum efficiency in LED devices even using stable aluminum electrodes. However, despite its interesting properties in this field, as to our knowledge, there is no report in the literature about the synthesis of the oligo(phenylene-vinylene-thiophene)s (OPVTs) containing with cyano groups on the vinylene linkage. Herein, we report the design and synthesis of a new family of functionalized OPVTs with definable skeletons that containing cyano groups at the various position of the vinylene moiety to strengthen the efficiency of the electron delocalization within conjugation skeletons. This design was aimed at producing an efficient red OPVT dye.

TP68

DIMETHYLZINC-INITIATED RADICAL ADDITION-CYCLIZATION OF ALKYLIDENE MALONATES

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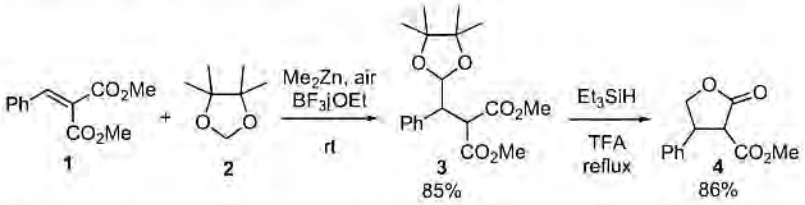
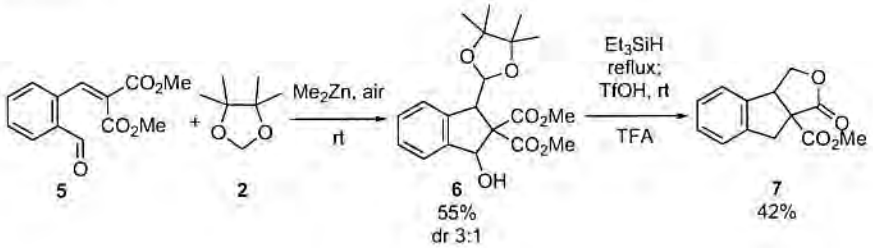
Conjugate addition-subsequent cyclization is the ideal process for multi-bond forming reaction. Realization of this kind of process requires, for example, C=C double bond selective conjugate addition of nucleophile to an aldehyde bearing Michael acceptor moiety and subsequent cyclization. Radical chemistry gave us one solution.
The reaction of acetal 2 with benzylidene malonate 1 was conducted in the presence of dimethylzinc and boron trifluoride-diethyl etherate under continuous introduction of air at rt for 2.5 h to give ether conjugate adducts 3 in 85% yield. Conversion of 3 into lactone 4 was performed in 86% yield.



Addition of 2 to *o*-formyl benzylidene malonate 5 was chemoselective to give cyclization product 6 with 3:1 dr in 55% yield. Treatment of 6 with triethylsilane and trifluoromethanesulfonic acid in trifluoroacetic acid gave tricyclic lactone 7 in 42% yield as a single stereoisomer.



TP69

SYNTHESIS OF FLUORESCENT SOLAMIN FOR VISUALIZATION OF CELL DISTRIBUTION

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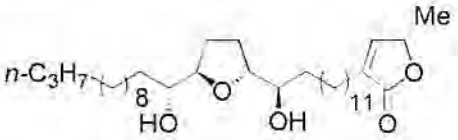
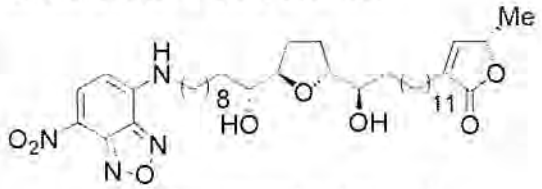
Annonaceous acetogenins are a family of natural products, which have attracted considerable attention by the interesting biological activities represented by potent cytotoxicity against human cancer cell lines. The mode of action was suspected to be based on its strong inhibitory activity against a mitochondrial complex I. However, the structure–activity relationship against the complex I inhibition was not completely related to its cytotoxicity. McLaughlin suggested that the mitochondrial assay is cell-free and does not take into consideration factors such as membrane transport, intracellular transport, metabolic inactivation, etc. To shed light on distribution of the annonaceous acetogenins within cells, fluorescently labeled acetogenin analogues were developed.[1,2] However, they lack the γ-lactone or THF moieties for the attachment of fluorescent label or simplification. This prompted us to synthesize a novel fluorescent annonaceous acetogenin retaining all functionalities.

We have developed a systematic and stereoselective synthesis of annonaceous acetogenins.[3] By applying this methodology, we planned to synthesize a novel fluorescent annonaceous acetogenin, which possesses all functional groups. Among many congeners, we selected solamin having a comparatively simple structure, but potent cytotoxicity against a wide range of cancer cell lines.[4] We planned to introduce the fluorescent tag at the end of the unfunctionalized hydrocarbon chain, because the γ-lactone, the THF, and the hydroxy moieties seem to play an important role in expression of biological activities in the acetogenin congeners. The 7-nitrobenzo[c][1,2,5]oxadiazol-4-yl)amino (NBD-NH-) group was employed as a fluorescent tag due to its strong fluorescence with long wavelength, that is advantageous to observe the cell distribution.

In this conference, a highly stereoselective synthesis of the NBD-labeled mono-THF annonaceous acetogenin, solamin bearing all functionalities will be presented.



solamin (**1**)



fluorescent solamin (**2**)

References:

1 Derbré S, Roué G, Poupon E, Susin SA, Hocquemiller R, ChemBioChem, 2005; 6, 979–982.

2 Liu HX, Huang GR, Zhang HM, Jiang S, Wu JR, Yao ZJ, ChemBioChem, 2007; 8, 172–177.

3 Maezaki N, Kojima N, Tanaka T, Synlett, 2006; 993–1003 and references cited therein.

4 Sinha SC, Keinan E, J. Am. Chem. Soc., 1993; 115, 4891–4892.

TP71

PARAMAGNETIC COMPLEXES FOR PROTEIN STRUCTURE DETERMINATION

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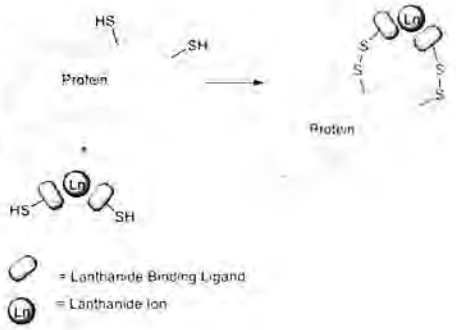
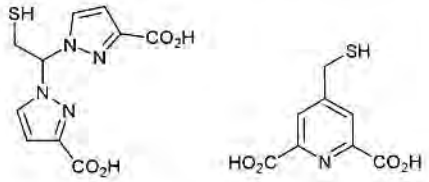
#Research School of Chemistry, Australian National University, Canberra, 2000

Paramagnetic tags in the form of metal complexes, attached to proteins can provide long range structural information within a protein that is otherwise not available. Lanthanide complexes are ideal for this work due their availability and their asymmetric chemical shifts. Through the interactions of the protein with the immobilized lanthanide complexes, the changes in the chemical shift in the NMR spectra can be used to calculate the protein structure.[1]

Two approaches are being used for the attachment of lanthanide complexes to proteins. The first approach uses the formation of disulfide bonds between the lanthanide complex and the protein to immobilize the complex while the second approach modifies the protein expression to incorporate lanthanide binding amino acids.

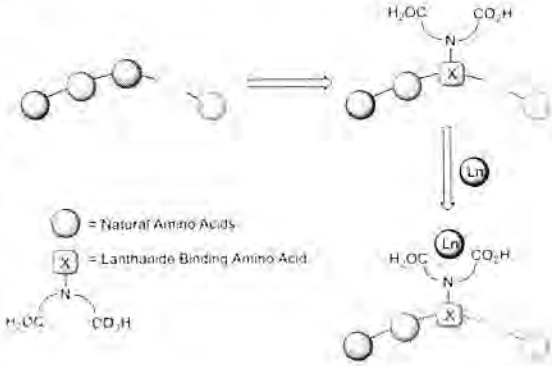
For the first method, a bis(3-pyrazolecarboxylic acid)methane 1 and 4-mercaptomethylpyridine-2,6-dicarboxylic acid 2 were identified as good lanthanide binding motifs. Their synthesis and preliminary NMR properties on proteins of interest will be discussed.

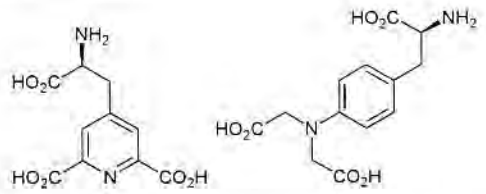




1 2

As part of the protein synthesis modification process, lanthanide binding amino acids are required. Two amino acids 3 and 4, based on the dipicolinic acid motif and iminodiacetic acid motif respectively have been proposed and the synthetic approaches to these ligands will be described.[2]





3 4

References:
(1) Pintacuda, G. John, M. Su, X. C. Otting, G. *Acc. Chem. Res.* 2007, *40*, 206-212.
(2) Wang, L. Schultz, P. G. *Angew. Chem. Int. Ed.* 2005, *44*, 34 - 66.

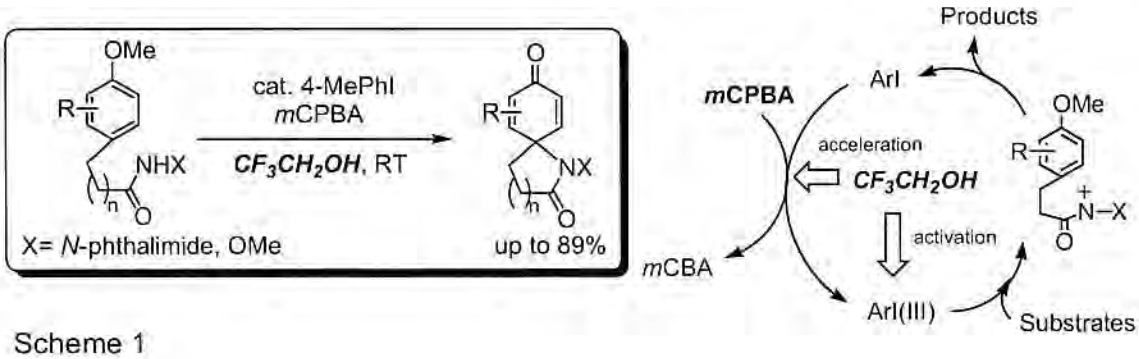
TP72

CATALYTIC UTILIZATION OF HYPERVALENT IODINE(III) REAGENTS: SPIRODIENONE FORMING REACTION IN FLUOROALCOHOL MEDIUM

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

Graduate School of Pharmaceutical Sciences, Osaka University, 1-6 Yamada-oka, Suita, Osaka, 565-0871 Japan

Hypervalent iodine reagents have attracted much attention due to their low toxicity, ready availability and similar reactivity to highly toxic heavy-metal oxidants. In view of recent demand for development of ecological chemical processes, many efforts have been devoted for effective use of the reagents over the past decades. We consider that realization of catalytic use of the stoichiometric reagents is indispensable for expanding their versatility and applicability in organic synthesis. With this respect, we have recently achieved the spirodienone lactone forming reaction of phenols with a catalytic amount of iodine(III) reagents,[1] by the selection of *m*CPBA as an appropriate co-oxidant for effective generation of hypervalent iodine(III) reagents.[2] However, the present system has one serious drawback, that is the necessity of strong acids such as trifluoroacetic acid and $BF_3 \cdot Et_2O$ in order to obtain high turn over number (TON). During our investigation for alternative mild catalytic conditions, we have established the successful introduction of fluoroalcohol medium, i.e. 2,2,2-trifluoroethanol (TFE), for replacing the previous strong acidic systems. Interestingly, it has been revealed that TFE here acts not only to activate the iodine(III) species but also to accelerate generation of the iodine(III) species during the reactions. On the basis of these findings we have now extended the catalytic strategy to the first hypervalent iodine(III)-catalyzed C-N bond forming reaction of amides via nitrenium ion intermediate, giving rise to synthetically important class of spirodienone lactams (Scheme 1).[3] These results will be presented in the poster session.



Scheme 1

References:

1) Dohi T., Maruyama A., Yoshimura M., Morimoto K., Tohma H., Kita Y. *Angew. Chem. Int. Ed.*, 2005; 44, 6193-6196.
2) Tohma H., Maruyama A., Maeda A., Maegawa T., Dohi T., Shiro M., Morita T., Kita Y. *Angew. Chem. Int. Ed.*, 2004; 44, 3595-3598; Dohi T., Maruyama A., Yoshimura M., Morimoto K., Tohma H., Shiro M., Kita Y. *Chem. Commun.*, 2005; 2205-2207.
3) Dohi T., Maruyama A., Minamitsuji Y., Takenaga N., Kita Y. *Chem. Commun.*, 2007; in press; *Chem. Sci.*, 2007; 4, C10.

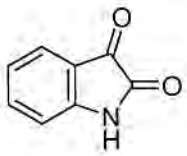
TP73

ISATIN DERIVATIVES AS NOVEL ANTI-CANCER AGENTS

Lidia Matesic,[a] John B. Bremner,[a] Stephen G. Pyne,[a] Julie M. Locke,[a] Marie Ranson[b] and Kara L. Vine[b]

[a]*Department of Chemistry, University of Wollongong, Wollongong NSW 2522, Australia*
[b]*School of Biological Sciences, University of Wollongong, Wollongong NSW 2522, Australia*

The synthetic versatility of isatin (1*H*-indole-2,3-dione) (1) has led to many bioactive derivatives including those with anti-cancer activities.[1-3] 5,7-Dibromoisatin (2) has been shown to possess modest cytotoxicity in a cell-based assay using human monocyte-like histiocytic lymphoma cells (U937) (IC_{50} 10.5 μM).[4] Derivatives of 5,7-dibromoisatin containing *N*-phenethyl, *N*-phenacyl and *N*-naphthylmethyl moieties have now been prepared since other work in the group had indicated similar compounds were cytotoxic against U937 cancer cells (unpublished results). The target compounds were assessed for their cytotoxicity *in vitro* and of the 11 compounds synthesised, two were found to exhibit IC_{50} values <1 μM against U937 cells. The synthesis and cytotoxicity evaluation of the isatins will be discussed, together with preliminary SAR work.



(1)

(2)

1. Moon MJ, Lee SK, Lee J-W, Song WK, Kim SW, Kim JI, Cho C, Choi SJ, Kim Y-C. *Bioorg. Med. Chem.*, 2006; 14, 237-246.
2. Abadi AH, Abou-Seri SM, Abdel-Rahman DE, Klein C, Lozach O, Meijer L. *Eur. J. Med. Chem.*, 2006; 41, 296-305.
3. Gursoy A, Karali N. *Eur. J. Med. Chem.*, 2003; 38, 633-643.
4. Vine KL, Locke JM, Ranson M, Benkendorff K, Pyne SG, Bremner JB. *Bioorg. Med. Chem.*, 2007; 15, 931-938.

TP74

SYNTHESIS OF BIS INDOLOMALEIMIDE DERIVATIVES WITH A SEVEN-MEMBERED CENTRAL RING

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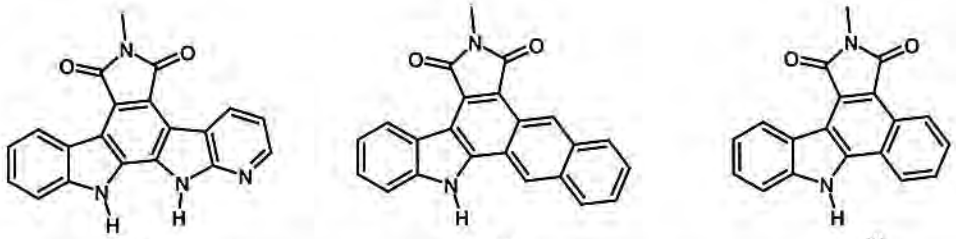
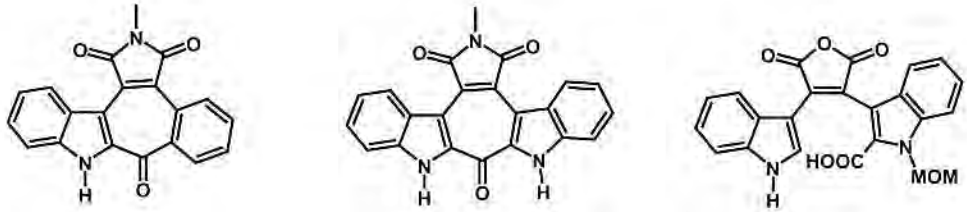
ICOA, BP 6759, Université d'Orléans, 45067 Orléans cedex 2, France

For some years we are interested in the synthesis of indolocarbazoles of type I-III [1-3] possesing biological activities.



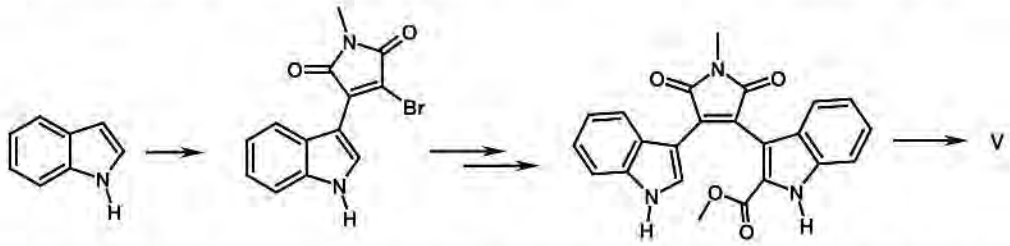
I II III

We have recently described the synthesis of compounds IV[4] showing a central tropolone ring instead of a fully aromatised structure like derivatives I-III. Here we want to present our recent results in the synthesis of bis indolo derivatives V and VI.



IV V VI

Starting from indole, compound V was obtained in five steps using *inter alia* a Stille reaction.



The influence of the protecting group on the indolic nitrogen atom on the course of the synthesis will be discussed.

References:

1 Routier, S. ; Mérour, J.-Y. ; Dias, N., Lansiaux, A. ; Bailly, C.; Lozach, O. ; Meijer L. *J ; Med. Chem.* 2006, *49*, 789-799.

2 Routier, S.; Peixoto, P.; Mérour J.-Y.; Coudert, G.; Dias, N.; Bailly, C.; Pierré, A.; Léonce, S.; Caignard, D.-H. *J ; Med. Chem.* 2005, *48*, 1401-1413.

3 Routier, S.; Ayerbe, N.; Mérour, J.-Y.; Coudert, G.; Bailly, C.; Pierré, A.; Pfeiffer, B.; Caignard D.-H.; Renard P. *Tetrahedron* 2002, *58*, 6621-6630.

4 Bourderioux, A. ; Routier, S. ; Bénéteau, V. ; Mérour, J. Y. *Tetrahedron Lett.* 2005, *46*, 6071-6074.

TP75

N-ACETYLNEURAMINATE LYASE AND DIHYDRODIPICOLINATE SYNTHASE ENZYMES: DO THEY SHARE HETEROCYCLIC INHIBITORS?

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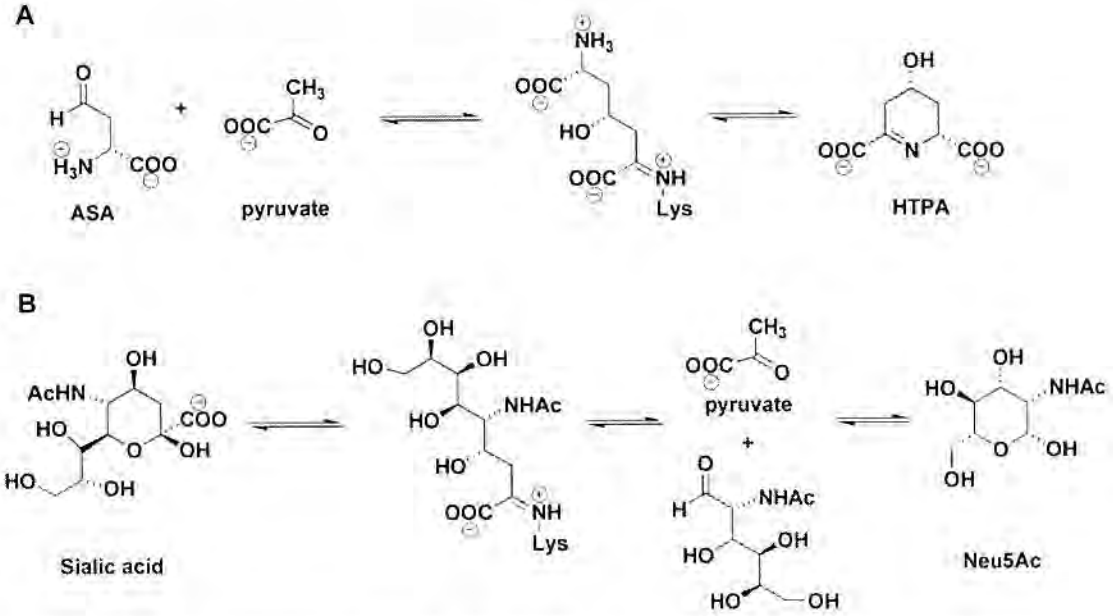
[1] *School of Chemistry and Bio21 Molecular Science and Biotechnology Institute, The University of Melbourne, Parkville, VIC, Australia*
[2] *School of Biological Sciences, University of Canterbury, Christchurch, New Zealand*

Our research team has a long standing interest in studying inhibitors of the lysine biosynthetic pathway as a potential new class of antibiotics. The first committed step in the lysine biosynthetic pathway is a process catalysed by the homotetrameric enzyme dihydrodipicolinate synthase (DHDPS), which, belongs to the *N*-acetylneuraminate lyase (NAL) sub-family of enzymes. The enzyme product formed by the DHDPS-catalysed reaction is the heterocycle HTPA (4-hydroxy-tetrahydrodipicolinate) and the product formed by the NAL-catalysed reaction is a sugar heterocycle (Scheme 1).[1]



Scheme 1. The reactions catalysed by **(A)** DHDPS and **(B)** NAL via Schiff-base intermediates.

To date we have only tested our inhibitor library that comprises heterocyclic product analogues against *E. coli* DHDPS.[2] This work extends to DHDPS from other pathogens (specifically, *Mycobacterium tuberculosis*, *Bacillus anthracis and* methicillin-resistant *Staphylococus* aureus) in order to establish the selectivity of potential new drugs. Compounds will also be screened against *E. coli* NAL, itself a drug target, in order to establish whether the heterocyclic compound library has application against this evolutionary related enzyme.

References:

1. Joerger, AC, Mayer, S, Fersht, AR, *Proc Natl Acad Sci U S A* 2003; 100, 5694-9.
2. Turner, JJ, Gerrard, J A, Hutton, C.A, *Bioorg Med Chem* 2005; 13, 2133-40.

TP76

SYNTHESIS AND FLUORESCENCE OF 2(1*H*)-PYRIDONES AND 2-METHOXYPYRIDINES IN SOLUTION AND IN SOLID STATE

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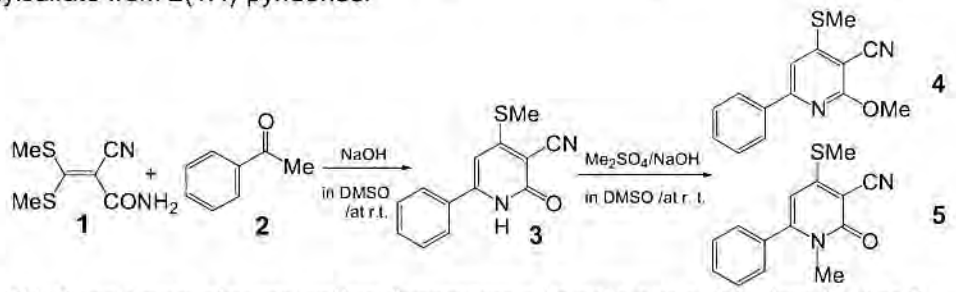
Recently, the structure-activity relationship of the fluorescent 2*H*-pyrones has been investigated and clarified.[1] On the other hand, we are interested in fluorescence of the various analogues of 2*H*-pyrones, in particular 2(1*H*)-pyridone that is an aza-analogues of 2*H*-pyrone may be indicated a new efficient fluorescent property from 2*H*-pyrone. The reaction of acetophenone (2) and 3,3-bis(methylsulfanyl)acryronitrile (1) was carried out in the presence of sodium hydroxide to give a desired compound; 2(1*H*)-pyridone (3).[2] Moreover, we obtained 2-methoxypyridines (4) and 1-methyl-2(1*H*)-pyridones (5) by general method using dimethylsulfate from 2(1*H*)-pyridones.



These 2(1*H*)-pyridones showed yellow fluorescence in solid state. Additionally, the 2-methoxypyridones showed fluorescence in solution. The preparation and fluorescence of 4-substituted 2(1*H*)-pyridones will be discussed.

References:

1) *a*) Mizuyama N, Tominaga Y, Kohra S, Ueda K, Hirayama S and Shigemitsu Y, *Bull. Chem. Soc. Jpn.*, 2006; 79, 602-611; *b*) Mizuyama N, Murakami Y, Nagaoka J, Kohra S, Ueda K, Hiraoka K, Shigemitsu Y and Tominaga Y, *Heterocycles*, 2006; 68, 1105-1108; *c*) Mizuyama N, Murakami Y, Kohra S, Ueda K, Nagaoka J, Takahashi K, Shigemitsu Y and Tominaga Y, *J. Heterocycl. Chem.*, 2007; 44, 115-132; *d*) Mizuyama N, Kohra S, Ueda K, Hiraoka K, Takahashi K and Tominaga Y, *Heterocycles*, 2007; 71, 399-409.
2) Tominaga Y, Kawabe M and Hosomi A, *J. Heterocycl. Chem.*, 1985; 37, 1325-1331.

TP77

CASCADE REARRANGEMENTS OF α-CYANO-γ-LACTONES PROMOTED BY DIAZOMETHANE

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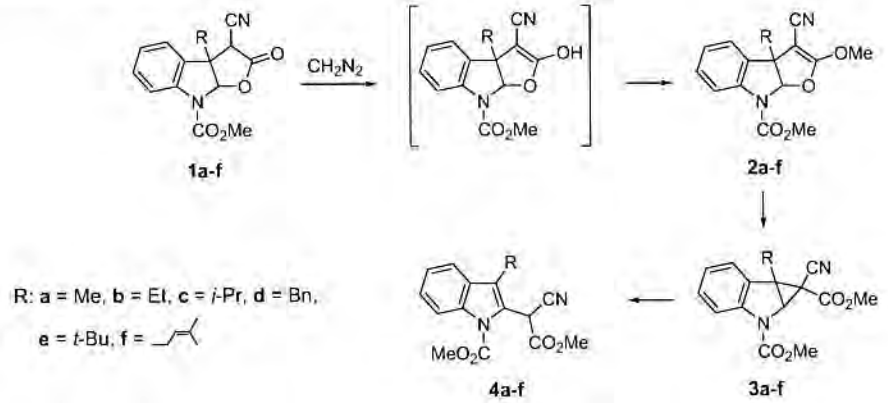
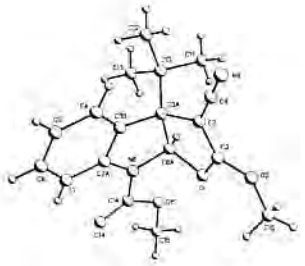
[a]*Departamento de Química y Sección Externa de Farmacología, Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional, Apartado 14-740, Mexico, D. F., 07000 Mexico.* [b] *Centro de Investigaciones Químicas, Universidad Autónoma del Estado de Hidalgo, Apartado 1-622, Pachuca, Hidalgo, 42001 Mexico* *smorales@cinvestav.mx*

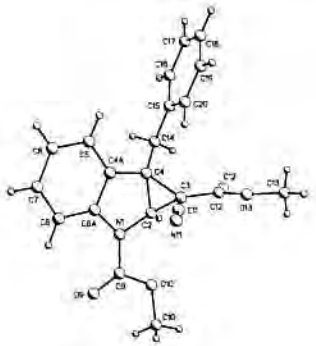
Sequential intermediates in the diazomethane induced conversion of indole α-ciano-γ-lactones 1a-f to 2-indolyl cyanomalonates 4a-f were isolated and purified by silica gel chromatography. These are: *i*) The ketene-*O*,*O*-dialkyl acetales 2a-f, resulting from *O*-methylation of the tautomeric enol lactones[1] with diazomethane. *ii*) The ring-contracted cycloprop[*b*]indoles 3a-f, which could result from vinyl acetal migration and ring cleavage. Finally, formation of 4a-f is believed to proceed by through-ring scission of the cyclopropane and concomitant loss of proton.[2]



The influence of the steric bulk of alkyl groups on the relative stability of intermediates 2a-f and 3a-f, arising from this unusually facile tandem process, was evaluated. The ^{1}H NMR monitored rearrangement of intermediates upon dissolution in $CDCl_3$ revealed that their stability decreased in the order: prenyl, *t*-Bu > Bn, *i*-Pr > Et > Me. The structures of novel compounds 2a-f, 3a-f and 4a-f were characterized by 2D NMR studies and by single-crystal X-ray analysis of compounds 2e and 3d.



2e



3d

1. Morales-Ríos MS, López-Camacho P, Suárez-Castillo OR, Joseph-Nathan P. *Tetrahedron Lett.*, 2007 (in press) doi: 10.1016/j.tetl 2007.02.006.
2. (a) Gibe R, Kerr MA. *J. Org. Chem.*, 2002, 67, 6247-6249. (b) Salim, M, Capretta A. *Tetrahedron*, 2000, 8063-8069. (c) Ikeda M, Matsugashita S, Tamura Y. *J. Chem Soc. Perkin I*, 1976, 2587-2590.

TP78

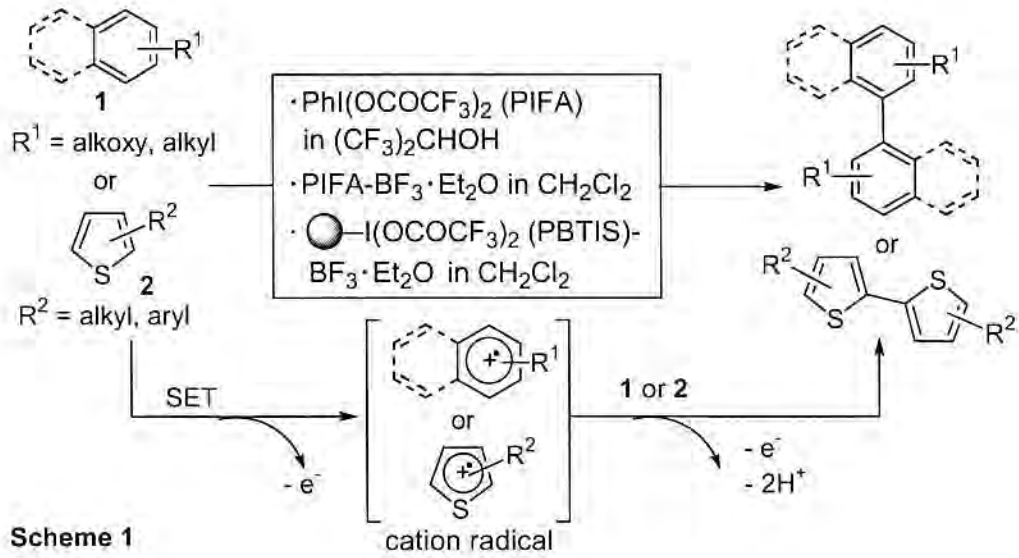
OXIDATIVE BIARYL COUPLING OF ELECTRONIC-RICH AROMATIC AND HETEROAROMATIC COMPOUNDS USING HYPERVALENT IODINE(□) REAGENTS

Koji Morimoto, Motoki Ito, Toshifumi Dohi, and Yasuyuki Kita

Graduate School of Pharmaceutical Sciences, Osaka University, 1-6, Yamada-oka, Suita, Osaka, 565-0871 Japan

Biaryl unit is a key building block in the structure of a large number of natural products and π-conjugated organic materials. Therefore, biaryl construction is one of the important subjects in organic synthesis. For electron-rich aromatic compounds, direct biaryl formation by oxidative methods is quite attractive and desirable, since it would not require any pre-functionalization of the substrate, i.e. halogenation, metallation, and so on.

Hypervalent iodine(III) reagents have been widely recognized as the safe and useful oxidants having reactivities similar to those of the highly toxic heavy metal oxidizers such as Pb(□), Tl(□), and Hg(□). Over the past decades, we have developed a variety of new and efficient transformations of electron-rich aromatic compounds using hypervalent iodine(III) reagents, and have succeeded in the oxidative coupling reaction of phenyl ethers and alkylarenes **1** involving the cation radical intermediates induced by phenyliodine bis(trifluoroacetate) (PIFA) in $(CF_3)_2CHOH$ or with the aid of BF_3□Et_2O (Scheme 1).[1] In the poster session, we would like to present a recent progress for the biaryl coupling method using hypervalent iodine(□) reagents, especially pertaining to the extension of the substrate scope and improvement of selectivity, by the exploration for the reagents and added Lewis acid.[2] The successful utilization of recyclable hypervalent iodine(□) alternatives to PIFA enhancing the practicability of the reaction is also described.



Scheme 1

References:

1) Tohma, H.; Morioka, H.; Takizawa, S.; Arisawa, M.; Kita, Y. *Tetrahedron*, 2001; 57, 345-352; Tohma, H.; Iwata, M.; Maegawa, T.; Kita, Y. *Tetrahedron Lett.*, 2002; 43, 9241-9244.

2) Dohi T.; Morimoto K.; Kiyono Y.; Maruyama A.; Tohma H.; Kita Y. *Chem. Commun.*, 2005; 2930-2932; Dohi, T.; Morimoto, K.; Maruyama, A.; Kita, Y. *Org. Lett.*, 2006; 8, 2007-2010.

TP79

SYNTHESIS OF NEW 1*H*,5*H*-THIAZOLO[5,4-*c*]QUINOLINE-2,4-DIONES

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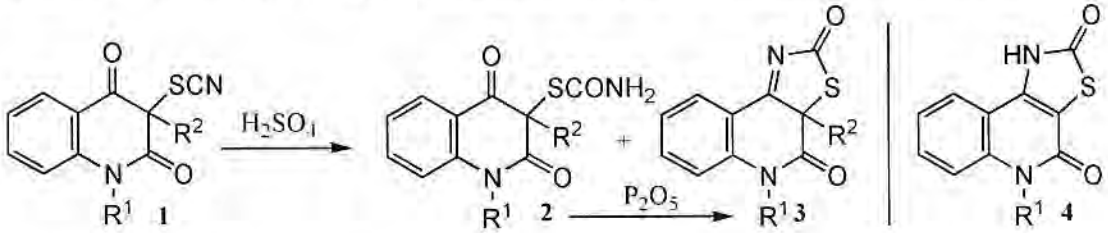
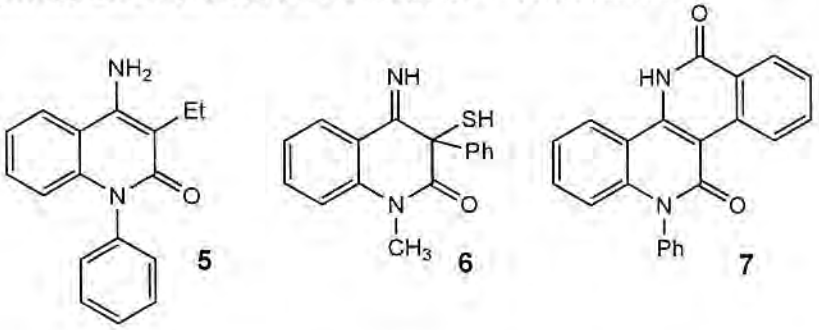
[a]*Department of Chemistry, Faculty of Technology, Tomas Bata University, CZ-76272 ZLÍN, Czech Republic*
[b]*Faculty of Chemistry and Chemical Technology, University of Ljubljana, SI-1000 Ljubljana, Slovenia*
mrkvicka@ft.utb.cz

We have recently reported that 3-thiocyanato-1*H*,3*H*-quinoline-2,4-diones (1) can be smoothly converted to the mixture of corresponding 3-carbamoylsulfanyl-1*H*,3*H*-quinoline-2,4-diones (2) and 3a*H*,5*H*-thiazolo[5,4-*c*]quinoline-2,4-diones (3) by the action of *conc.* sulfuric acid.[1]



The proportion of compounds 3 and 2 can be increased by the addition of a small quantity of phosphorus pentoxide to the reaction mixture. However, if the amount of phosphorus pentoxide was too high, several different types of compounds arose, the structure of which depends on the character of substitution in starting compounds 1.
In the case R^1 = H or alkyl and R^2 = alkyl, novel [1,3]-thiazolo[5,4-*c*]quinoline-2,4-(1*H*,5*H*)-diones (4) are produced. Compounds 4 are very stable and exhibit melting points above 400°C.
In the case R^1 = phenyl and R^2 = ethyl, 4-amino-3-ethyl-1-phenyl-1*H*-quinoline-2-one (5) was obtained.
Using compound 1 with substitution R^1 = methyl and R^2 = phenyl, 4-imino-1-methyl-3-phenyl-3-sulfanyl-3,4-dihydroquinolin-2(1*H*)-one (6) was isolated.
In last observed case, if both substituents were phenyl groups, the reaction leads to the formation of 8-phenyl-1*H*,8*H*-isoquinolin[4,3-*c*]quinolin-2,7-diones (7). The proposal of the reaction mechanism of these transformations will be discussed.



Acknowledgements:
This study was supported by the Ministry of Education Youth and Sports of the Czech Republic (Grant No. MSM 7088352101), the Ministry of Education, Science and Sport, Republic of Slovenia (Grant No. P0-0503-0113), and The Czech Science Foundation (Grants No. 203/07/P266 and Grant No. 203/07/0320).

References:
[1] Klásek A., Polis J., Mrkvička V., Kosmrlj J., *J. Heterocyclic Chem.* 2002, *39*, 1315-1320.

TP80

NEW THREE-COMPONENT REACTION: FORMATION OF SEVEN-MEMBERED RING BY AN UNEXPECTED REACTION AT THE γ-POSITION OF THE β-KETO ESTER

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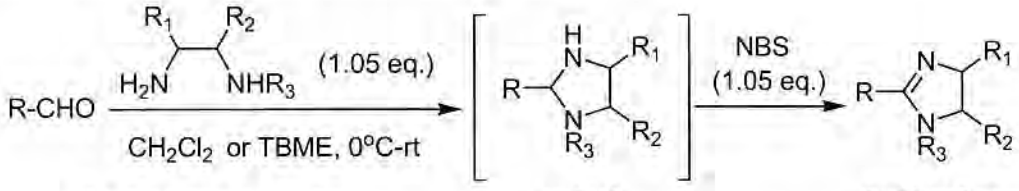
The studies regarding multicomponent reactions (MCRs) have been receiving much attention because of their efficiency and diversity of products. They are very useful in the drug discovery process and powerful tools for the total synthesis of complex natural products. Therefore, the development of a new MCR is an important subject in the fields of medicinal and organic chemistries.

Recently we reported a novel one-pot synthesis of imidazolines from aldehydes and diamines through oxidation of aminal intermediates by NBS.[1)]

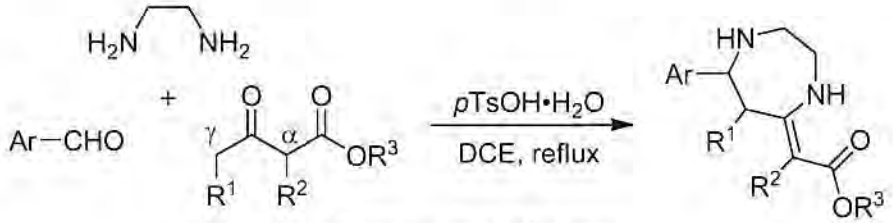


One-Pot Operation

As part of these studies, we realized the unexpected reactivity of the β-keto ester, and developed the novel three-component reaction of aromatic aldehydes, ethylenediamine and β-keto esters to produce [1,4] azepane compounds having enamino esters.

This reaction is very interesting in the reactivity of the β-keto esters. Thus, in our reaction β-keto esters react at their γ-position contrary to the general α-selectivity of the addition of β-keto esters. The products of this reaction are also very useful because they have both secondary amine and enamino esters, which enable further modifications leading to molecular diversity.

In this presentation, we will show the detail of this reaction including the experimental study and the application of the products to other heterocyclic compounds.



R^1, R^2= H or alkyl, R^3= alkyl

References:

1) Fujioka, H.; Murai, K.; Ohba, Y.; Hiramatsu, A.; Kita, Y. *Tetrahedron Lett.*, 2005; 46, 2197-2199.; Fujioka, H.; Murai, K.; Kubo, O.; Ohba, Y.; Kita, Y. *Tetrahedron*, 2007; 63, 638-643.

TP81

BENZOFURAN CONSTRUCTION AND ITS SYNTHETIC APPLICATION

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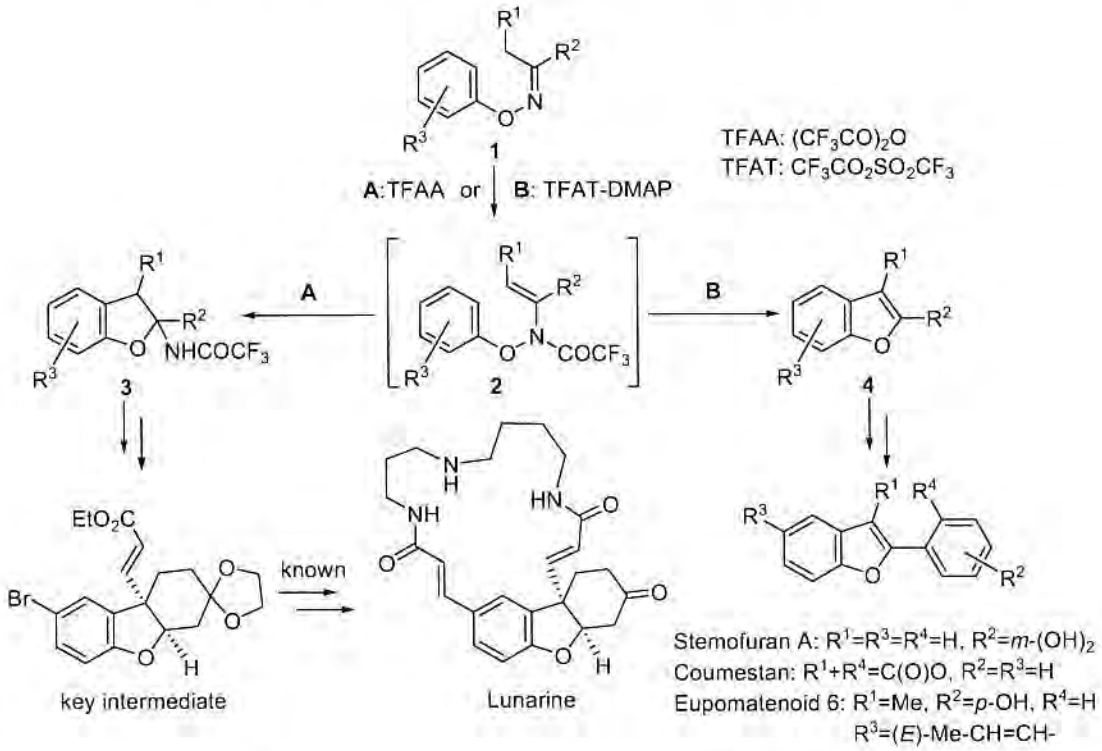
4-19-1, Motoyamakita, Higashinada, Kobe 658-8558, Japan

Benzo[b]furans are attractive target compounds of organic synthesis because they are widely found in nature as partial structures of oxygen containing heterocycles and exhibiting unique biological activities. We have recently developed a novel and practical synthesis of benzofurans 3 and 4 via the route involving [3,3]-sigmatropic rearrangement of *N*-trifluoroacetyl enehydroxylamines 2 as an intermediate.
Treatment of oxime ethers 1 with trifluoroacetic anhydride (TFAA) gave dihydrobenzofurans 3 while reaction of the identical oxime ethers 1 with trifluoroacetyl triflate (TFAT) in the presence of DMAP afforded aromatized benzofurans 4 without the isolation of plausible enehydroxylamines 2. It is noteworthy that either dihydrobenzofurans 3 or benzofurans 4 can be formed selectively from the same substrate by changing only the reagent.



Synthetic utility of this reagent-controlled benzofuran construction methodology is demonstrated by the synthesis of two types of natural benzofurans. One is the formal total synthesis of Lunarin which carries a quaternary carbon in benzofuran structure.[1] The other is short synthesis of biologically active 2-arylbenzofurans such as Stemofuran A, Eupomatenoid 6 and Coumestan.[2]
This reaction would provide an efficient synthetic method of not only natural benzofurans but also the related biologically active lead compounds for medicines.[3]

References:
1. Takeda, N., Miyata, O., Kitamura, M., Kagehira, S., Naito, T., *Synlett*, 2006; 3415-3418.
2. Miyata, O., Takeda, N., Naito, T., *Org. Lett.*, 2004; *6*, 1761-1763.
3. Takeda, N., Miyata, O., Naito, T., *Eur. J. Org. Chem.*, 2007;1491-1509.

TP82

ADDITION OF SULFUR MONOXIDE "SO" TO ALKENES AND ALKYNES: FORMATION OF THIIRANE OXIDES AND THIIRENE 1-OXIDES

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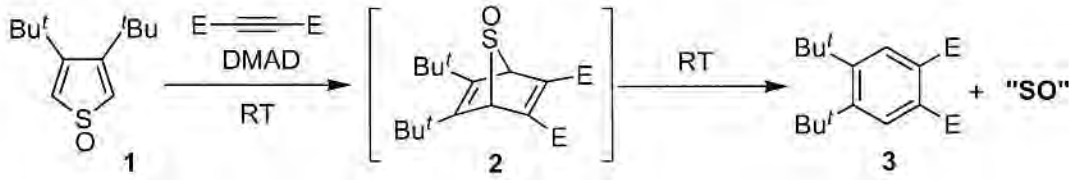
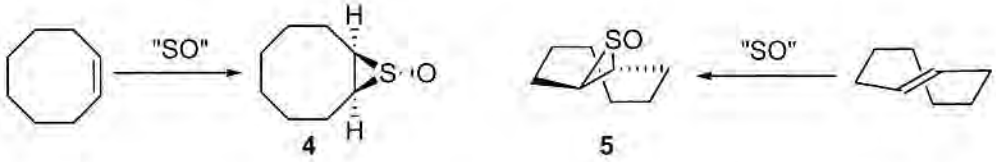
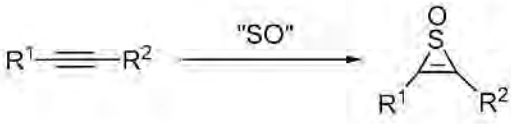
The Diels-Alder adduct 2, produced by reaction of 3,4-di-*tert*-butylthiophene 1-oxide 1 with dimethyl acetylendicaboxylate (DMAD) at room temperature, extrudes sulfur monoxide "SO" spontaneously with formation the phathalate 3. The "SO" generated by this method added to alkenes and alkynes to provide thiirane oxides and thiirene 1-oxides, respectively.



Thus, the reaction of 1 with DMAD in the presence of a series of alkenes (excess) provided the corresponding thiirane oxides though in modest yields. Seemingly, the addition is stereoselective as exemplified by addition to *cis*- and *trans*-cyclooctenes that produced 4 and 5, respectively.
It also added to alkynes thus providing the most straightforward synthesis of thiirene 1-oxide. The reaction allowed the preparation of structurally simple thiirene 1-oxides such as 6c-d.





6a: $R^1 = R^2$ = 1-adamantyl
6b: $R^1 = R^2$ = Ph
6c: $R^1 = R^2$ = Me
6d: R^1 = Ph, R^2 = H
6e: R^1 = *tert*-Bu, R^2 = H

TP83

FIBROUS MATERIALS BASED ON POLYACRILONITRILE DERIVATIVES AND HETEROMETALLIC COMPLEXEX OF SOME d-ELEMENTS

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The general principle of the synthesis of fibrous inorganic ion-exchanging composites, containing the combination of polymer analogous conversion reactions of the fibres and cycles of ion-molecular layering is advanced [1]. Synthesis of thin nanomolecular layers of the Cu(II) and Fe(III) ferrocyanides on surface of the polyacrylonitrile fibres was performed on the basis of this principle. The synthesis of thin layers of Cu(II) and Fe(III) hexacyanoferrates (II) was performed by the method of the chemosorption layering on a matrix which represented the derivatives of polyacrylonitrile fibres containing $HO–N=\dot{C}–NH_2$ groups with the degree of substitution of CN-groups about 50% [2]. The synthesized materials were studied while using methods for chemical and X-ray analyses, electronic-microscopy, IR-spectroscopy and sorption investigations. According to the data from the X-ray studying of the synthesized pellicular hexacyanoferrates, their composition is described by the formulas $K_x Cu_{(2-x)} [Fe(CN)_6] \cdot 4H_2O$ and $K_x Fe_{(4-x)} [Fe(CN)_6]_3$ (compounds I and II respectively). By the method of X-ray analysis it was stated that the formed pellicular inorganic layers have a crystalline structure. By the methods of IR-spectroscopy, formation of heteroatomic cycles by polyacrylonitrile derivatives (with participation of strong H-bonds) was shown. They were capable to disintegrate under the effect of the ions of d-metals. It is suggested that strong adhesion of the layers with the matrix is caused by formation of linkage between $[Fe(CN)_6]^{4-}$-ions and the ions in chelates' composition through CN-bridges. The equilibrium ion-exchange capacity on the Rubidium, Cesium, Strontium and Thallium ions linearly depends on the layer's thickness, which is determined by the number of layering cycles (n) and reach maximum when n = 8. The ion-exchange property testing of the synthesized compositions on the basis of the Cu(II) and Fe(III) ferrocyanides was carried out by sorption from water solutions of the strontium ions and stable and radioactive Cesium isotopes. The investigation of ion-exchange kinetics of $^{137}Cs^+$-ions into K^+-ions was carried out by the method of limited volume while using of a semiconductor multichannel gamma-spectrometer for measurement of solution specific activity. The equality of the ionite ion-exchange capacity both on ion Strontium, and on ion Cesium is observed under fourfold cycle layering. S-shape nature of curve of such dependence was determined. It is shown that the process of the ion exchange proceeding in two stages. The full ion-exchange capacity of ionites on the basis Cu(II) and Fe(III) ferrocyanides reaches 1,0 mmol-equ/g. Ion-exchange equilibrium on synthesized ionites is reached approximately 30 times faster, than on corresponding powdery crystalline ferrocyanides. It was revealed that distribution coefficients of $^{137}Cs^+$-ions for Cu(II) and Fe(III) hexacyanoferrates are 17000 and 12000 respectively. This indicates the prospect of their practical use in some ion-exchange processes – for example, in extraction of radionuclides from the waste, in deactivation and purification of waste waters.

References:

1. Nesterenko V.P. et al, *Abstracts, The XVI Mendeleev Congress on General and Applied Chemistry, Moscow, Russia*, 1998; 2, 415.
2. Nesterenko V.P. et al, *Book of Abstracts, The XXXIII International Conference on Coordination Chemistry "The Chemistry of Metal Ions in Everyday Life". Florence, Italy*, 1998; 389.

TP84

METAL TRIFLATE-CATALYZED FRIEDEL–CRAFTS REACTION OF FURAN DERIVATIVES USING BENZYLIC ALCOHOLS

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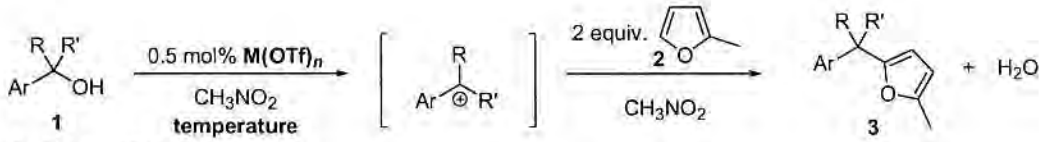
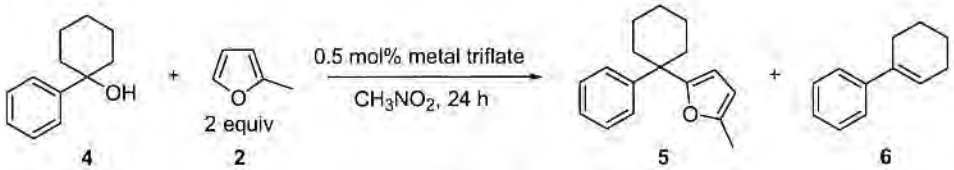
Furan derivatives have been widely used as synthetic synthons as dicarbonyl compounds, oxoenoic acids, and carboxylic acids.[1] Many applications are known in the field of the natural products syntheses. Furylaldehydes and lithiofurans have been used for the introduction of furan rings.

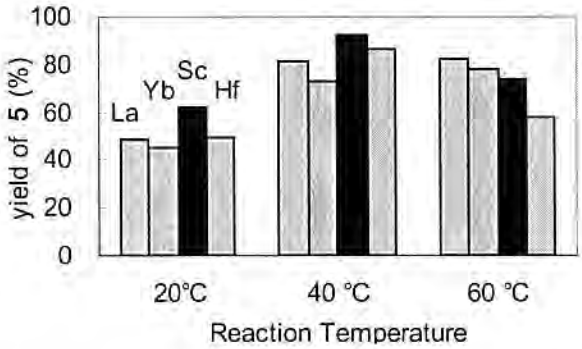
We have developed a highly effective Friedel-Crats-type benzylation system for aromatic nucleophiles using benzylic alcohols catalyzed by hafnium and rare-earth metal triflates in nitromethane.[2] The benzylation of 2-methylfuran (**2**) smoothly proceeded without using anhydrous conditions to give benzylated furan derivatives **3** in high yield. Various benzylic alcohols bearing a functional group on their aromatic rings (e.g, 4-MeO-, 4-BnO-, 4-CbzNH-, 4-Cl), 1-(2-furyl)ethanol, and 1-(2-thienyl)ethanol were able to be used for the Friedel-Crafts reaction.



Ar: Ph, naphthyl, heteroaromatic

Construction of a benzylic quarternary carbon center was also achieved using tertiary benzylic alcohols. Tertiary benzylic alcohol **4** easily decomposed into the olefin **6** at higher temperature. Optimization of the reaction conditions were easily carried out by catalyst-temperature screenings. The $Sc(OTf)_3$-catalyzed reaction at 40 °C gave **5** in high yield. Other examples of secondary and tertiary benzylated furan derivatives will be reported.





References:
(1) (a) Lipshutz B. H. *Chem. Rev.*, 1986; 86, 795-819. (b) Rassu G. Zanardi F. Battistini L. Casiraghi G. *Chem. Soc. Rev.*, 2000; 29, 109-118. (c) Burke M. D. Berger E. M. Schreiber S. L. *J. Am. Chem.* Soc., 2004; 126, 14095-14104.
(2) Noji M. Ohno T. Fuji K. Futaba N. Tajima H. Ishii K. *J. Org. Chem.*, 2003; 68, 9340-9347.

TP85

SYNTHESIS AND CHARACTERIZATION OF A METALLO-SUPRAMOLECULAR CAPSULE UTILIZING A CYCLIC-PEPTIDE SCAFFOLD.

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School of Chemistry, The University of Sydney, NSW 2006, Australia
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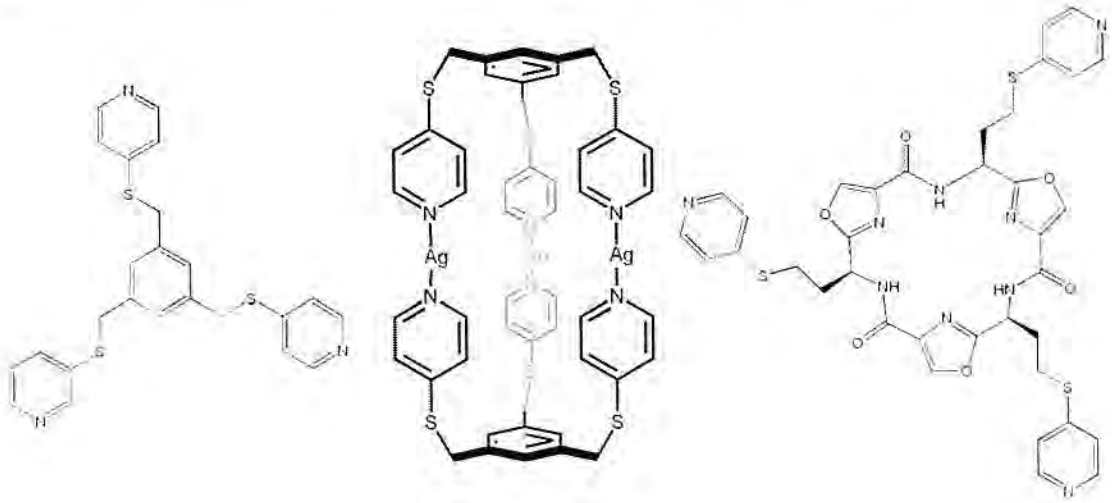
Over the past few decades the use of supramolecular chemistry has been a popular approach to form pre-determined architecture. We are particularly interested in incorporating silver (I) into capsules, which we previously reported for a simpler tripolal pyridyl ligand (1). [1] This afforded a capsule of formula $Ag_3(1)_2(NO_3)_3$ (2) (Figure 1). The present study is also a tripodal system, using a cyclic peptide scaffold, to which can be appended three pendant arms containing donor groups. This allows us create similar capsules with a larger interior volume, different coordinating functional groups and different metals.

The research presented here describes the synthesis of our novel cyclic peptide scaffold (3), as wellas its functionalisation with a variety of donor groups and and metal complexation studies.



(1) (2) (3)

Figure 1

References:
1. Bray DJ, Liao LL, Antonioli B, Gloe K, Lindoy LF, McMurtrie JC, Wei G, Zhang XY . *List Dalton Trans.*, 2005; 2082-2083

TP86

THE SELECTIVE PREPARATION OF PARTIAL CONE O-ARYL CALIX[4]ARENE ETHERS FROM 1,3-DIMETHOXYCALIX[4]ARENE: A NEW PLATFORM FOR THE PREPARATION OF NON-AGGREGATED DYES

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Aggregation between phthalocyanines has wide ranging implications for a variety of applications such as PDT, sensing and catalysis. We are particularly interested in preparing a new generation of phthalocyanines that possess lower aggregational behaviour; such phthalocyanines should demonstrate enhanced materials performance. Previous workers have introduced dendrimers into the peripheral benzo groups of phthalocyanine [1], these new systems demonstrated low aggregation, we believed we could improve on these novel systems by introducing a more rigid structure into the peripheral groups of the Pc. Our substituent of choice was tetra-t-butylcalix[4]arene, a large rigid macrocycle that we believed could introduce the necessary steric bulk required to significantly lower aggregation.
The research presented here describes the synthesis of new and novel t-butyl calix[4]arene substituted phthalocyanines. A variety of different derivatives have been prepared an example of one, a tetra-substituted calix[4]arene phthalocyanine 1, is outlined in Figure 1. Aggregational behaviour has been studied by both ^{1}HNMR and UV-VIS methods for all derivatives made.

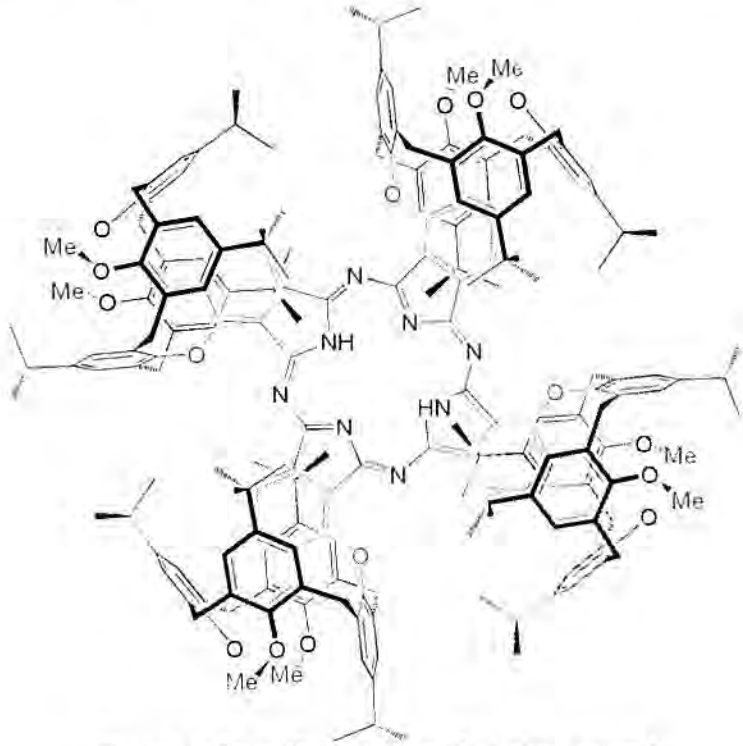


Figure 1.: Tetra Calix[4]arene Phthalocyanine 1

References:
1 (a) Kernag, C. A.; McGrath, D. V. *Chem Comm.*, 2003, 1048-1049 *(b)* Helliwell, M.; Mckeown, N. B.; Reynolds, S.; Shawcross, A. *Tetrahedron Lett.*, 2001, 42, 813-816

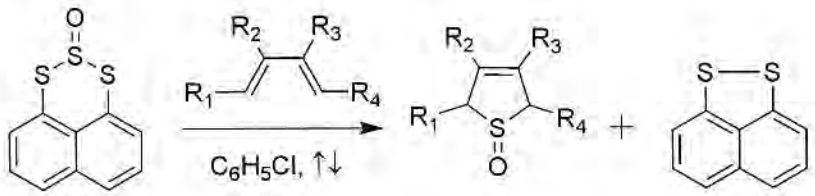
TP87

SYNTHESIS AND APPLICATION OF NOVEL SULFUR MONOXIDE TRANSFER REAGENTS

Richard S. Grainger* and Bhaven Patel

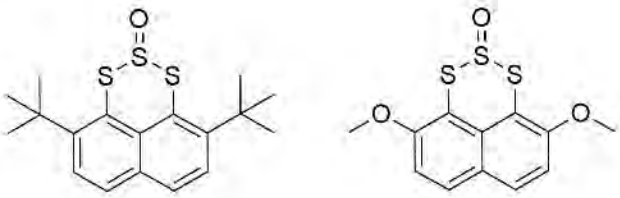
School of Chemistry, University of Birmingham, Edgbaston, Birmingham, B15 2TT, UK.

Sulfur monoxide (SO) is an unstable gas that rapidly disproportionates in the gas phase.[1] 1, 8-Naphthalene fused trisulfide-2-oxide (1) has recently been prepared in our group as a sulfur monoxide transfer reagent.[2] Heating 1 in the presence of dienes results in the formation of dihydrothiophene-S-oxides (2) and the recyclable by-product disulfide (3). Sulfoxides (2) have been transformed into thiophenes via a Pummerer reaction.



1 2 3

In this poster we present evidence (kinetic studies and trapping experiments) that the reaction of (1) with dienes is consistent with the generation of free SO followed by in situ trapping. We also report the synthesis and reactivity of trisulfide oxides 4 and 5 designed to probe the role of steric and electronic effects in the thermal elimination of SO.



4 5

References:
1. Hartzell, GE.; Paige, JN. *J. Org. Chem.*, 1967; 32, 459-460.
2. Grainger, RS.; Procopio, A.; Steed, JW. *Org Lett.*, 2001; 3, 3565-3568.

TP90

APPLICATION OF *D*-ERYTHRONOLACTONE AS THE KEY CHIRAL BUILDING BLOCK TO THE TOTAL SYNTHESIS OF AIGIALOMYCIN D

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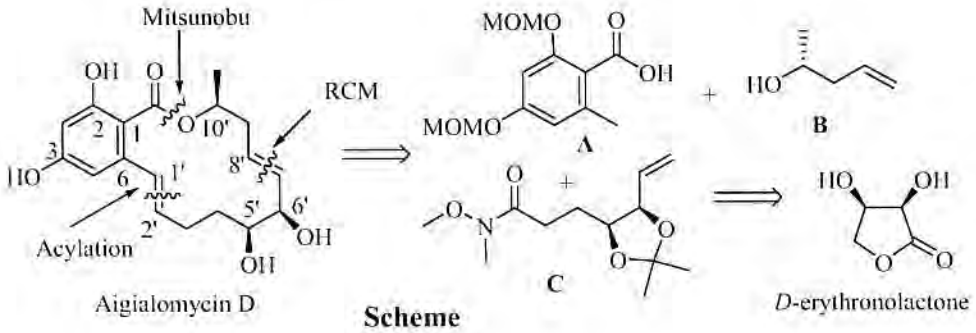
Aigialomycin D, which possesses potent antitumour and anti-malarial activity, is a member of a class of 14-membered resorcyclic macrolides recently isolated from the marine mangrove fungus *Aigialus parvus* BCC5311.[1] Three total syntheses of this compound have been reported so far.[2,3,4] We are interested in developing a more efficient and practical route for the synthesis of aigialomycin D and its analogues using readily available starting materials. Herein we present a three-component (A-C) convergent total synthesis of aigialomycin D which are highly efficient and could be industrially applicable. (Scheme) This efficient synthesis, which has a longest linear sequence of only 10 steps with 19% overall yield, features the use of *D*-erythronolactone as the key chiral building block for the synthesis of fragment C. Assembly of the fragments by the Mitsunobu reaction between A and B and acylation at C1' with C, followed by olefin ring closing metathesis (RCM) completed the synthesis of the macrocycle.



Scheme

(1) Isaka M., Suyarnsestakorn C., Tanticharoen M., *J. Org. Chem.* 2002; 67, 1561.
(2) Geng X., Danishefsky S. J., *Org. Lett.* 2004, 6, 413.
(3) Barluenga, S.; Dakas, P.-Y.; Ferandin, Y.; Meijer, L.; Winssinger, N. *Angew. Chem. Int. Ed.* 2006; 45, 3951.
(4) Lu, J.; Ma, J.; Xie, X.; Chen, B.; Shea, X.; Pan, X. *Tetrahedron: Asymmetry*, 2006; 17, 1066.

TP93

STUDIES TOWARDS THE TOTAL SYNTHESIS OF SCH-64874, ARANOTIN, AND RELATED NATURAL PRODUCTS

Ben Cebon[1]; Mark Rizzacasa[1]; Keith Watson[2]; Jonathan Baell[2].

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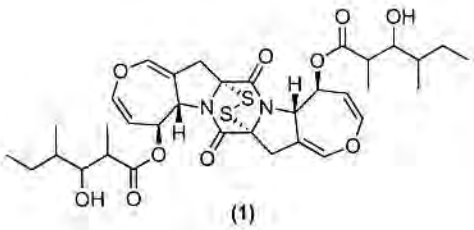
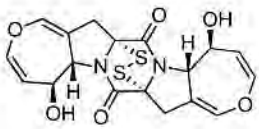
[2]*The Walter and Eliza Hall Institute of Medical Research, Parkville, Australia*

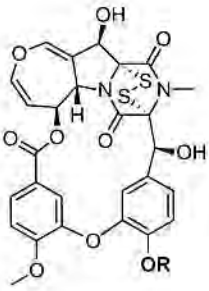
The epidithiodiketopiperazine core has been discovered in numerous natural products, isolated from a wide range of fungal and microbial sources. Family members possess exciting antiviral, antibiotic, antitumour, and immunomodulating activity. Of particular interest are compounds containing a dihydrooxepin system. These include SCH-64874 (1), which is closely related to aranotin (2), and is a potent inhibitor (IC_{50} = 1.5μM) of the epidermal growth factor receptor.[1, 2] Also of interest is MPC-1001 (3), a derivative of emestrin (4) which has displayed single-digit nM antiproliferative activity against the DU145 human prostate cancer cell line.[3] An approach to the total synthesis of these compounds will be presented, which relies on the formation of the oxepin ring utilising a novel Diels-Alder / *retro*-Diels-Alder sequence.



(1)



(2)



(3) : R = Me
(4) : R = H

References:

1. Hegde VR; Dai P; Patel M; Das PR; Puar MS. *Tetrahedron Lett.* 1997; 38(6), 911-914.

2. Nagarajan R; Huckstep LL; Lively DH; DeLong DC; Marsh MM; Neuss N. *J. Am. Chem. Soc.* 1968; 90(11), 2980-2982.

3. Onodera H; Hasegawa A; Tsumagari N; Nakai R; Ogawa T; Kanda Y; *Org. Lett.* 2004; 6(22), 4101-4104.

TP94

STUDIES TOWARDS THE SYNTHESIS OF THE AJUDAZOLS

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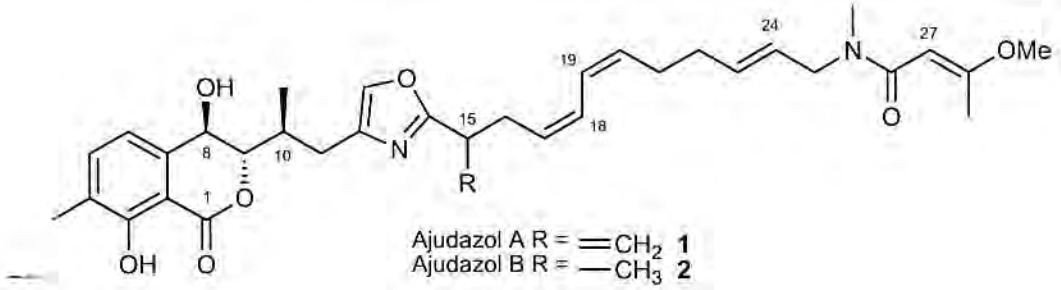
School of Chemistry, Bio21 Molecular Science and Biotechnology Institute, The University of Melbourne, Vi, Australia

The ajudazols are novel myxobacterial metabolites which were isolated from Chondromyces crocatus in 2002.[1] During secondary biological screening, both ajudazols showed only minor activity against a few fungi and Gram-positive bacteria, but displayed 50% inhibition of NADH oxidation in beef heart submitochondrial particles at a concentration of 22.0 nM for ajudazol A (1) and 18.4 nM for ajudazol B (2).[2] These promising results, along with their unique structures, make the ajudazols inviting targets for total synthesis. The tri-substituted isochromanone core of the ajudazols is extended by an oxazole ring, a highly unsaturated aliphatic C15-C25 chain and a terminal 3-methoxybutenamide moiety. While the relative configuration of the C8-C10 stereotriad has been determined, the absolute stereochemistry is currently unknown. Furthermore, the stereochemistry of the remote C15 chiral centre of ajudazol B (2) remains undetermined. We anticipate that all stereochemical questions could be answered by a total synthesis of the ajudazols. Our progress towards the synthesis of the ajudazols will be described.



References:
1) Jansen R, Kunze B, Reichenbach H, Höfle G. *Eur. J. Org. Chem.*, 2002, 917.
2) Kunze B, Jansen R, Höfle G, Reichenbach H. *J. Antibiot.*, 2004, *57*, 15

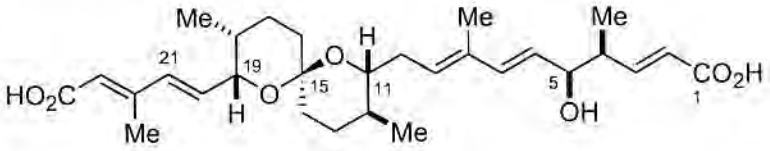
TP95

STUDIES TOWARDS THE SYNTHESIS OF THE SPIROFUNGINS

Lynch, J; Zanatta; S. D.; Rizzacasa, M A

Bio21 Molecular Science and Biotechnology Institute, School of Chemistry, The University of Melbourne, Melbourne, Vic, Australia

The spirofungins are a novel polyketide-spiroketal-type antifungal antibiotics isolated in a 4:1 mixture of spiroisomers from *Streptomyces violaceuniger* Tü 4113.[1] Spirofungins showed a high inhibition activity against yeasts and some fungi such as the human pathogen *Candida albicans* and a moderate antifungal activity against filamentous fungi such as *Botrytis cinerea* and *Mucos miehei*.[2] The biological activities and their unique structures, make the spirofungins interesting targets for total synthesis. The spirofungins posses a 6,6 spiroketal core, seven stereogenic centres and a C(11) triene acid and C(19) diene acid side chains. Spirofungin A (1) is epimeric to spirofungin B (2) at the C(15) spirocarbon.[3,4] Progress towards the total synthesis of the spirofungins using cross metathesis to construct the spiroketal fragment will be reported.



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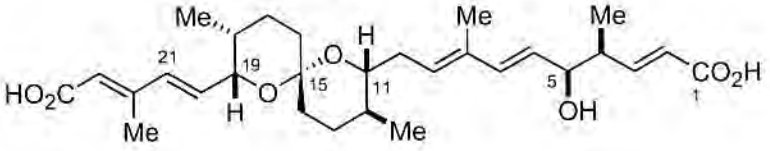

2

References:

1. Holtzel, A.; Kempter, C.; Metzger, J. W.; Jung, G.; Groth, I.; Fritz, T.; Fiedler, H.-P. *J. Antibiot.* 1998, *51*, 699.
2. Takahashi, H.; Osada, H.; Koshino, H.; Kudo, T.; Amano, S.;Shimizu, S.; Yoshihama, M.; Isono, K. *J. Antibiot.* 1992, *45*, 1409.
3. Zanatta, S. D.; White, J. M.; Rizzacasa, M. A. *Org. Lett.* 2004, *6*, 1041.
4. Shimizu,T.; Satoh, T.; Murakoshi, K.; Sodeoka, M. *Org. Lett.* 2005, *7*, 5573.

TP96

STUDIES TOWARDS THE SYNTHESIS OF CITRAFUNGIN A

Tsegay, S.; Rizzacasa, M. A.

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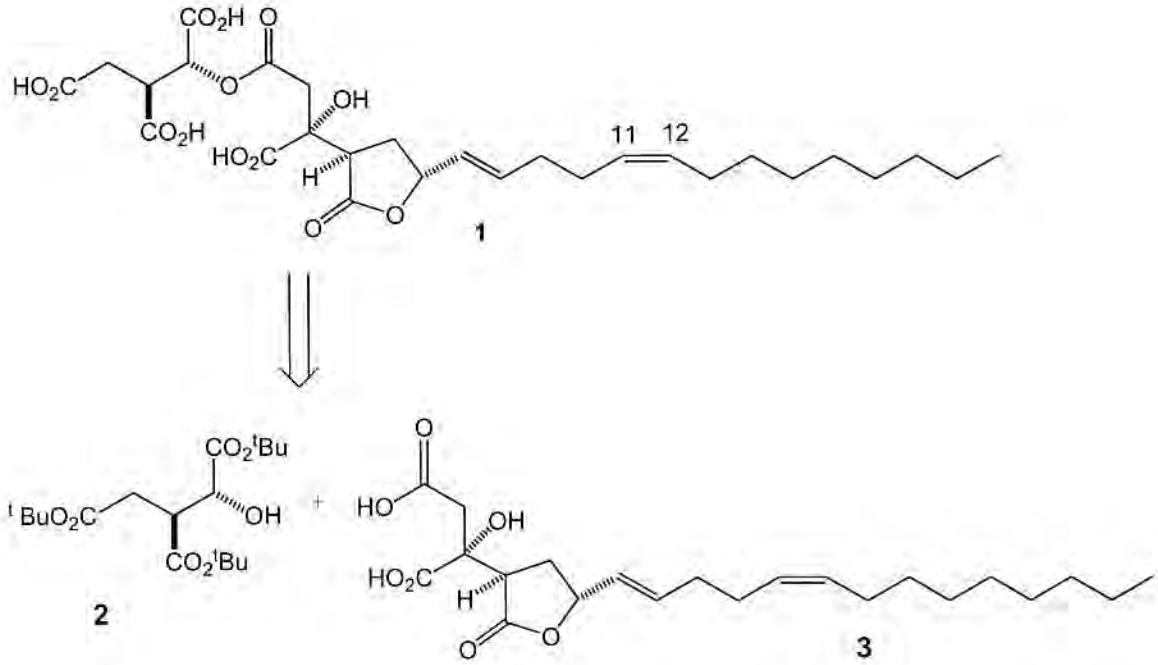
Citrafungin A (1) is a naturally-occurring alkylcitrate derivative that was discovered in the fungal fermentation extracts of sterile mycelia isolated from cow dung collected in Alaska.[1] Citrafungin A (1) is known to inhibit the GGTase activity of various pathogenic fungal strains with an IC_{50} of 2.5-15 μM and shows antifungal activity[1] with an MIC of 0.43-55 μM.[1] GGTase is an enzyme present in *Saccharomyces cerevisiae* that catalyses an essential reaction in which a specific lipid group, lipids that have terminating with a CaaX motif such as Rho1p acting as a substrate, becomes covalently attached (prenylation) to proteins involved in cell growth and differentiation, allowing these proteins to associate with the cell membrane and proper function.[2] Our progress towards the synthesis of citrafungin A (1) from fragments 2 and 3 will be discussed in this poster.



References:

1 Singh, S. B.; Zink, D. L.; Doss, G. A.; Polishook, J. D.; Ruby, C.; Register, E.; Kelly, T. M.; Bonfiglio, C.; Williamson, J. M.; Kelly, R.; *Org. Lett.* 2004, *6*, 337

2 Jeffrey S. Taylor, T. Scott Reid, Kimberly L. Terry, Patrick J. Casey and Lorena S. Beese, *EMBO J.* 2003, *22*, 5963.

TP97

UNEXPECTED FORMATION OF ε- AND γ-LACTAMS FROM β-AMINOESTER USING *T*-BULI

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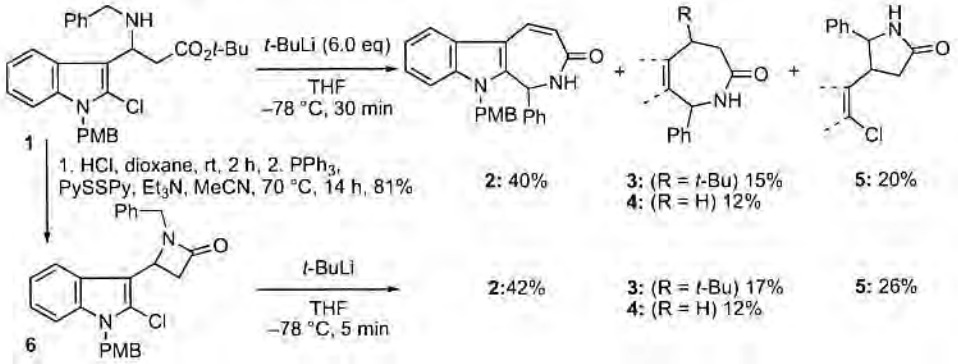
We have been engaged in the synthesis of chiral β-aminoesters through the asymmetric conjugate addition of lithium amides to α,β-unsaturated esters.[1] Aiming at functionalization of the 2-position on the indole ring via Li-halogen exchange reaction, we treated β-aminoester 1 with *t*-BuLi. We surprised to find that the products were ε- and γ-lactums 2-5.

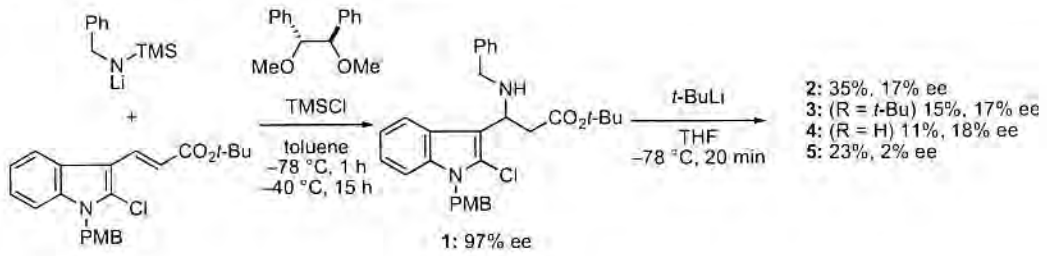
To a solution of 1 in THF at –78 °C under Ar was added *t*-BuLi. After the mixture was stirred for 0.5 h at –78 °C, the mixture of ε- and γ-lactams 2-5 were obtained.

Since LDA has been known to cause the ring expansion of β-lactams to ε- and γ-lactams,[2] we assumed that this unusual reaction preceeded by the formation of β-lactam followed by ring expansion reaction.

In fact, treatment of β-lactam 6, prepared from 1 by conversion to carboxylic acid followed by cyclization, with *t*-BuLi gave 2-5 in similar yields.



We then investigated whether chirality transfer was possible or not. Chiral diether ligand-catalyzed asymmetric conjugate addition of lithium amide[1] gave the chiral β-aminoester 1 with 97% ee. Treatment of 1 with *t*-BuLi gave rise to racemic γ-lactam 5. The chirality of 1 was partially transferred to ε-lactams 2-4 with 17-18% ee.



References

1. a) Doi, H.; Sakai, T.; Iguchi, M.; Yamada, K.; Tomioka, K. *J. Am. Chem. Soc.* 2003, *125*, 2886-2887. b) Sakai, T.; Doi, H.; Tomioka, K. *Tetrahedron* 2006, *62*, 8351-8359 and references therein.
2. Durst, T.; Elzen, R. V. D.; LeBelle, M. J. *J. Am. Chem. Soc.* 1972, *94*, 9261-9263.

TP98

EXPLORING THE SCOPE OF PSEUDOPROLINE-ASSISTED PEPTIDE CYCLIZATION

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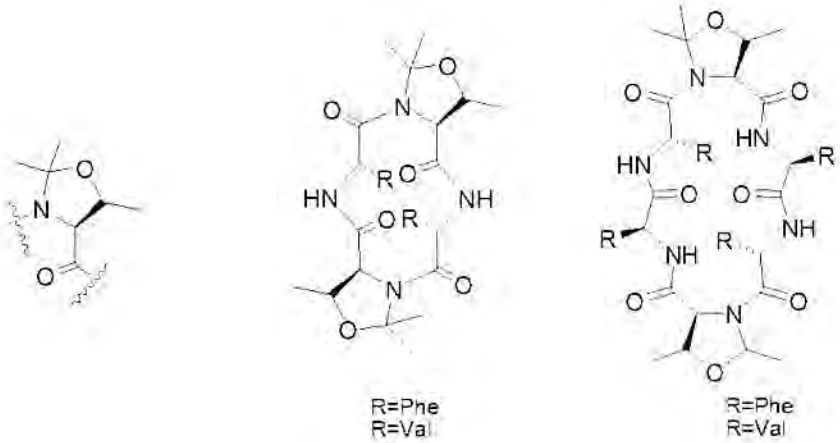
School of Chemistry, The University of Sydney, NSW, Australia

The synthesis of cyclic peptides and derivatives is currently of significant interest, due to their potential applications in a range of areas spanning both chemistry and biology. Cyclic peptides exhibit a wide range of biological activities and a particular advantage of their cyclic structure is a higher resistance to enzymatic degradation than their linear counterparts. Additionally, the restricted conformational flexibility of cyclic peptides allows them to present functional groups in a spatially well-defined manner and has been of great importance in the study of bioactive protein conformations.[1]

Unfortunately, the head-to-tail cyclisation of a linear peptide is often a slow, low-yielding reaction, accompanied by undesired side reactions such as cyclodimerisation and pimerization.[2] We have recently developed a new method for peptide cyclisation that utilizes removable turn-inducers, in the form of pseudoprolines (1), to encourage the linear peptide precursor to adopt a conformation that is amenable to cyclisation.[3,4] We are currently investigating the scope of this methodology by cyclising linear peptides of different size and sequence (2,3,4,5).



References:
1. For recent reviews see (a) Lambert, J. N.; Mitchell, J. P.; Roberts, K. D. *Perkin Trans. 1*, 2001, 471; (b) Davies, J. S. *J. Pept. Sci.*, 2003, *9*, 471.
2. Kopple, K. D. *J. Pharm. Sci*, 1972, *61*, 1345.
3. Skropeta, D.; Jolliffe, K. A.; Turner, P. *J. Org. Chem.*, 2004, *68*, 8804.
4. Sayyadi, N. ; Skropeta, D.; Jolliffe, K. A.; *Org. Lett.*, 2005, *7, 549*

TP99

MULTICOMPONENT SYNTHESIS AND FOLLOW-UP CHEMISTRY OF ISOCYANO CONTAINING DIHYDROPYRIDONES

R. Scheffelaar, M. Paravidino, J. D. Muilwijk, A. Znabet, F. J. J. de Kanter, M. B. Groen, R. V .A. Orru

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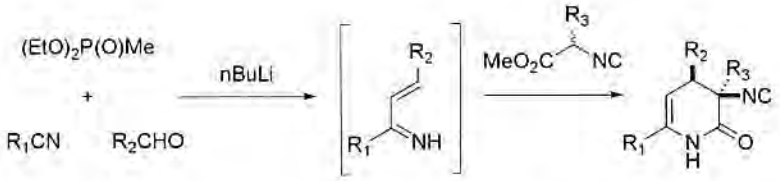
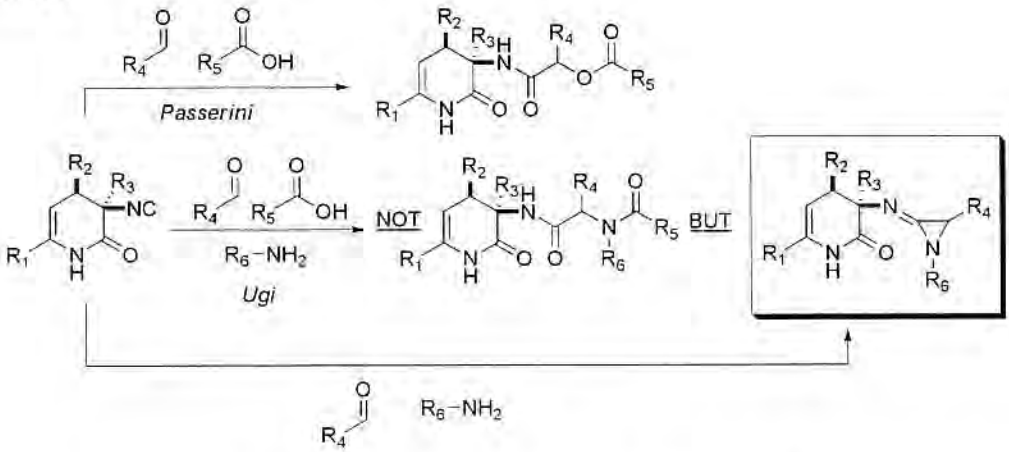
In the course of a programme directed towards the search for new multicomponent methodologies to access valuable heterocyclic scaffolds,[1-2] a new and efficient route to isocyano containing 3,4-dihydro-2-pyridones has been developed and explored.[3] Multicomponent reactions that lead to heterocycles containing isocyano substituents are unprecedented and offer the possibility for further differentiation, like follow-up isocyanide based multicomponent chemistry.

Scheme 1



The new methodology is based on a Horner-Wadsworth-Emmons condensation between a phosphonate, a nitrile, and an aldehyde to afford a 1-azadiene intermediate (Scheme 1). The latter is trapped *in situ* by a suitable isocyanoacetate to give the desired heterocyclic scaffold through a cyclocondensation reaction. The reaction showed to be highly diastereoselective and variation of nearly all components proved successful.
Moreover the new multicomponent reaction has been combined with the Passerini and Ugi reaction (Scheme 2). Surprisingly, the latter gave not the expected Ugi-product though the new and unique iminoaziridine scaffold.

Scheme 2



1. Bon, R.S.; Vliet van, B.; Sprenkels, N.E.; Schmitz, R.F.; de Kanter, F.J.J.; Stevens, C.V.; Swart, M.; Bickelhaupt, F.M.; Groen, M.B.; Orru, R.V.A. *J. Org.Chem.*, **2005**, *70*, 3542-3553.
2. Vugts, D.J.; koningstein, M.M. ; Schmitz, R.F.; de Kanter, F.J.J.; ; Groen, M.B. Orru, R.V.A., *Chem. Eur. J.*, **2006**, *12*, 7178-7189.
3. Paravidino, M.; Bon, R.S.; Scheffelaar, R.; Vugts, D.J.; Znabet, A.; Schmitz, R.F.; de Kanter, F.J.J.; Lutz, M.; Spek, A.L.; Groen, M.B.; Orru, R.V.A. *Org. Lett.*, **2006**, *23*, 5369-5372.

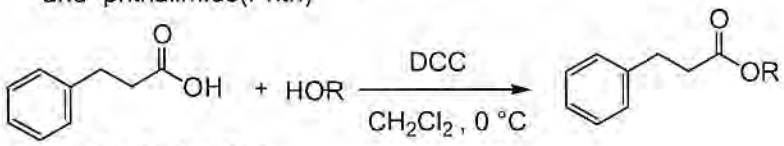
TP100

PREPARATION AND REACTIVITIES OF *N*-(3-PHENYLPROPIONYLOXY)-BENZOTRIAZOLE, - BENZOTHIAZOLE, AND -PHTHALIMIDE TOWARD SEVERAL NUCLEOPHILES

Md. Chanmiya Sheikh; Shunsuke Takagi; Tatsuya Mori; Mebumi Sakai; Asako Ogasawara; Satoru Fukumoto and Hiroyuki Morita*
Department of Material Systems Engineering and life Science, Faculty of Engineering, University of Toyama, 3190 Gofuku, Toyama 930-8555, Japan

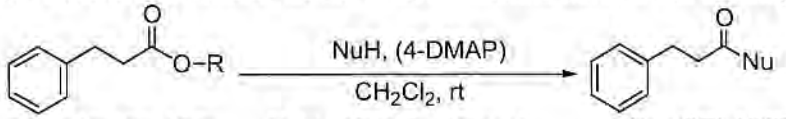
N-(3-Phenylpropionyloxy)-benzotriazole(Bt), -benzothiazole(Btz), and -phthalimide(Phth) were prepared by the reaction of *N*-(Hydroxy)-benzotriazole(Bt), -benzothiazole(Btz), and -phthalimide (Phth) with hydrocinnamic acid in the presence of DCC. In order to develop new class of non-symmetry cross-linkers, the reactivities of these model compounds with alcohols, phenol, amines, and thiols were carried out for comparison. It was revealed to exhibit the order of the *N*-(3-Phenylpropionyloxy)-benzotriazole, -benzothiazole, and - phthalimide; Bt > Btz > Phth. Details mentioned above will be presented and discussed.

Scheme. Preparation of *N*-(3-Phenylpropionyloxy)-benzotriazole(Bt), -benzothiazole(Btz), and -phthalimide(Phth)



R = Bt, Btz, Phth

Table. Reactions of Several Active Ester Derivatives with Various Nucleophiles



R = Bt, Btz, Phth NuH : Alcohols, Phenol, Amines, Thiols Nu : OR', NHR', SR'

entry	NuH	(R = Bt) time	(R = Bt) yield(%)	(R = Btz) time	(R = Btz) yield(%)	(R = Phth) time	(R = Phth) yield(%)
1	BnOH	5 min	77	7 min	91	24 h	82
2	$PhCH(CH_3)OH$	40 min	77	90 min	78	3 days	46
3	Ph_2CHOH	1 h	79	5 h	74	3 days	39
4	$BnNH_2$	2 min	99[a]	5 min	92[a]	8 min	93[a]
5	BnSH	2 min	98	6 min	98	8 min	97
6	Phenol	5 min	79	8 min	98	6 h	78

[a] reaction proceeded without base

TP101

SYNTHETIC STUDIES OF REVEROMYCIN A: NOVEL PREPARATION OF THE SUCCINATES OF TERTIARY ALCOHOLS

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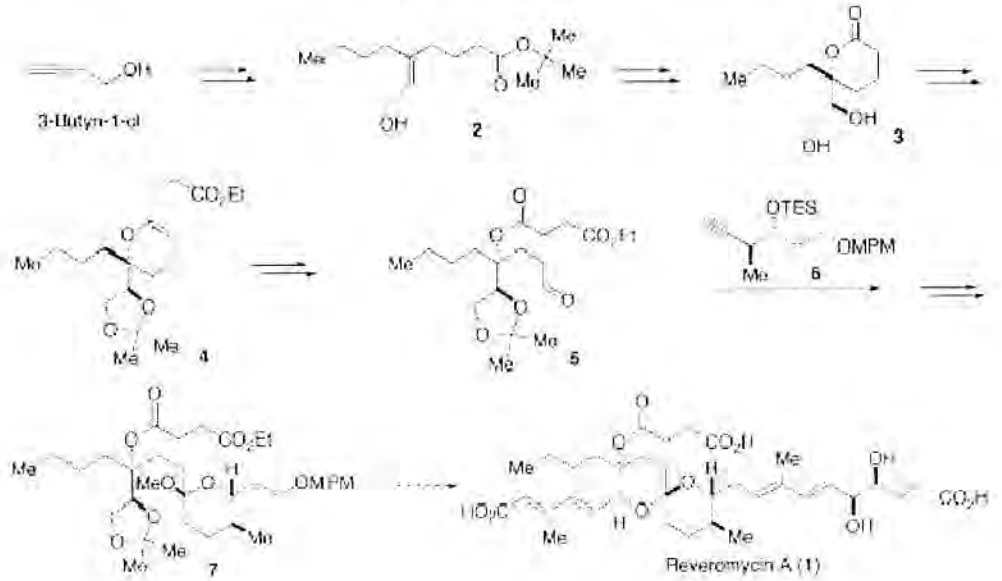
Reveromycin A (1) is a polyketide-type antibiotic isolated from the genus *Streptomyces* as an inhibitor of mitogenic activity induced by the epidermal growth factor (EGF).[1] The molecular target of 1 was identified as isoleucyl-tRNA synthetase (IleRS).[2] The characteristic structural feature of 1 includes a 1,7-dioxaspiro[5.5]undecane moiety, that is, the 6,6-spiroketal core bearing a hemisuccinate, two unsaturated carboxylic acid side chains and two alkyl groups.[3] From its strong biological activity as a potential drug for treatment of tumor, hyperpotassemia and bone disease and its synthetically challenging molecular architecture, the first asymmetric total synthesis of 1 was accomplished by our group using the succinylation of tertiary alcohols under high pressure as a key step.[4] Now, we have developed a new methodology for the synthesis of the succinates of tertiary alcohols without troublesome high pressure.

Namely, 3-butyn-1-ol was converted into the lactone 3 through the Sharpless asymmetric epoxidation of 2 in 14% overall yield in eleven steps. After protection of the hydroxyl groups, the dihydropyran 4 was prepared via palladium-catalyzed coupling of the ketene acetal triflate derived from 3 and zinc derivative. Successive oxidation of 4 with OsO_4 and $Pb(OAc)_4$ gave the succinyl derivative 5, which was then converted into the methyl ketal 7 via the coupling of 5 and 6. Synthesis of 1 from 7 is in progress. These results will be discussed.



References:

1. Takahashi, H.; Osada, H.; Koshino, H.; Kudo T.; Amano, S.; Shimizu, S.; Yoshihama, M.; Isono, K. *J. Antibiot.* 1992, *45*, 1409-1413.
2. Miyamoto, Y.; Machida, K.; Mizunuma, M.; Emoto, Y.; Sato, N.; Miyahara, K.;Usui, T.; Osada, H.; Takahashi, H.; Hirata, D.; Miyakawa, T. *J. Biol. Chem.*, 2002, *277*, 28810-28814.
3. Koshino, H.; Takahashi, H.; Osada, H.; Isono, K. *J. Antibiot.* 1992, *45*, 1420-1427.
4. Shimizu, T.; Masuda, T.; Hiramoto, K.; Nakata, T. *Org. Lett.* 2000, 2, 2153-2156.

TP102

A NEW PROCESS FOR PRODUCING 2-HALO-4-NITROIMIDAZOLES *VIA* HALOGEN EXCHANGE REACTIONS

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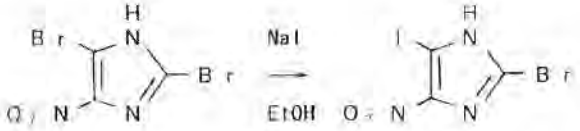
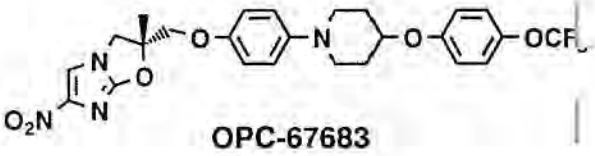
Tubercular patients have been steadily increasing in recent years, because mutant tubercle bacillus becomes resistant against chemotherapeutic agents. Spreading of drug resistant tubercle bacillus is a problem one should not ignore. We are taking a positive approach to the problem and we hope on OPC-67683 as a new antituberculous agent having high activities against drug resistant tubercle bacillus.
2-Halo-4-nitroimidazoles have been used for important synthetic intermediates of OPC-67683, and the production will be expected on a large scale in the near future. Preliminary attempts to obtain 2-halo-4-nitroimidazoles have already been reported. 1,4-Dinitroimidazole is reported to give 2-chloro- 4-nitroimidazole *via* 2,4-dinitroimidazole by refluxing with chlorobenzene followed by heating with hydrochloric acid.[1)] However, the use of explosive dinitroimidazole is a serious problem for practical use. An improved process for producing 2-bromo-4-nitroimidazole was accomplished recently, *via* selective reduction of *N*-alkoxymethyl-2,5-dibromo-4-nitro-imidazoles.[2)]
Here, we wish to report on the latest results of our investigations which provide safety practical procedures for producing 2-halo-4-nitroimidazoles. 2-Bromo-4-nitroimidazole was found to be easily prepared in a good yield by treating 2,5-dibromo-4-nitroimidazole with NaI followed by catalytic hydrogenation. The selective replacement of 5-position bromine atom of 2,5-dibromo-4-nitroimidazole by iodine atom was easily accomplished by the action of NaI (2eq). The resulting 2-bromo-5-iode-4-nitroimidazole was hydrogenated in the presence of a Pd catalyst under mild conditions[2)] to give 2-bromo-4-nitroimidazole in a good yield. The new process which we have developed offer improved yields, safety operations, and simplified procedures for the production of 2-halo-4-nitroimidazoles, and found suitable for practical application.





References:
1) Suwinski J., Salwinske E., Watras J., and Widel M., *Pol. J. Chem.*, 1982; 56, 1261-1272.
2) Goto F., Takemura N., Ohtani T., Hasegawa T., Tsubouchi H., Utsumi N., Fujita S., Kuroda H., Shizuta T.,
and Sasaki H. (Otsuka Pharmaceutical Co., Ltd.), *JPN Kokai Tokkyo Koho*, JP2004-269500.

TP103

NOVEL PORPHYRIN-ANTIBIOTIC CONJUGATES FOR TARGETED INHIBITION OF *PORPHYROMONAS GINGIVALIS*

Benjamin C.M. Yap[a], Grace Simpkins[a], Maxwell J. Crossley[a] and Neil Hunter[b]

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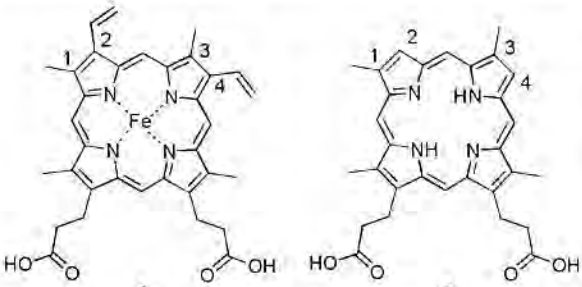
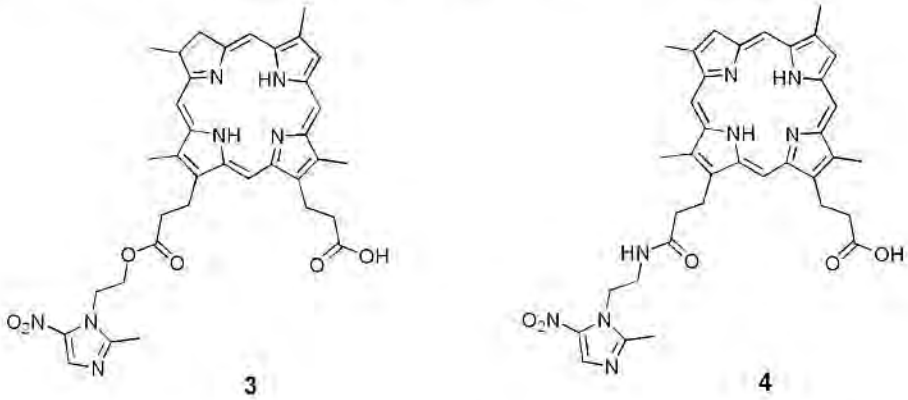
The black-pigmented gram-negative anaerobe *Porphyromonas gingivalis* is a key etiological agent of periodontal disease. This bacterium has been reported to display an absolute requirement for either hemin 1 or hemoglobin as growth factors in the gingival crevice. The capacity of porphyrins to sustain the growth of *P. gingivalis* is related to recognition by a sub-domain protein HA2 of the porphyrin macrocycle in an iron-independent manner; the recognition process appears to be unique.[1]

Previous work has shown that there are certain requirements for recognition of the porphyrin macrocycle by HA2. Changes in the functional groups at positions 1, 2 and 4 of the vinyl face of the porphyrin macrocycle are tolerated whereas changes at position 3 are incompatible with recognition by HA2. In addition, a free propionic acid on the porphyrin macrocycle is necessary for this recognition.[2] It is possible, therefore, to target HA2 with porphyrin analogues that resemble hemin 1 such as deuteroporphyrin IX (DPIX, 2).



The aim of the research is to boost the uptake of the antibiotic into *P. gingivalis* to enhance antibacterial activity and increase selectivity for the pathogen. The avenue for this is using porphyrins as "Trojan horses" to transport a known antibiotic, metronidazole, into the cell. In this work, metronidazole was attached to DPIX 2 by an ester bond to give 3 and metronidazole amine was attached to DPIX 2 through an amide bond to give 4. The recognition, acquisition and utilization of these porphyrin-antibiotic conjugates by *P. gingivalis* will be reported.



References:
1. Hunter N, Nguyen K-A, McDonald JA, Quinn MJ, Langley DB, Crossley MJ and Collyer CA, *J. Porphyrins Phthalocyanines*, 2002; *6*, 774-782.
2. Paramaesvaran M, Nguyen KA, Caldon E, McDonald JA, Najdi S, Gonzaga G, Langley DB, DeCarlo A, Crossley MJ, Hunter N and Collyer CA, *J. Bacteriol.*, 2003; *185*, 2528-2537.

TP104

SYNTHESIS AND ANTI- MICROBIAL ACTIVITY STUDY ON COMPLEXES OF 2 -AMBI WITH CU (II), ZN (II) CD (II) SALTS

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Department of Chemistry,Dr. H. S.Gour University Sagar M.P.

Complexes of 2-AMBI with Cu(II), Zn (II) and Cd (II) chloride have been synthesized. They have been characterized by elemental analysis, conductivity measurement, IR and PMR spectral studies and Screned for antimicrobial activity. The result shows that complexes are non electrolytes two and four coordinated the ligands acts as monodentate and show good to moderate antimicrobial activity. Benzimidazole and its derivatives play an important role in analysis and in several biological reaction Benzimidazole as its 5,6 dimethyl derivative occurs in vitamin B_{12}. In addition to this benzimidazole derivatives exhibit antibacterial, anthelmintic and insecticidal activities [1-5]. Transition metal complexes containing bezimaidazoles are widely used as catalysts of hydrogenation hydroformaylation oxidation and other reactions [6-9]. We report hare the synthesis and characterization of 2- (amino methyl) benzimidazole (L), its complexes with Cu(II), Zn (II) and Cd (II) salt and antimicrobial activity of its complexes

TP105

SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 4-ARYL -5-(ARYL HYDRAZINE CARBAMOYL)-6 METHYL -1,3,4 TRI HYDRO PYRIMIDINE-2-ONES DERIVATIVES

Ramandeep Kumar Singh*,Rahul Bardia, Anil Ahirwar, A.P.Prajapati, J. T. Rao

and Y. Rohan

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Hydropyrimidines and hydrazine derivative are reported to posses diverse biological activity keeping this in view, we have undertaken the synthesis and antimicrobial activities of some pyrimidine derivatives.

Aromatic aldehyde undergo *Biginati's* reaction to give pyrimidine derivatives. Which react with various hydrazine derivatives to form the titled compounds (2). Aldehyde used was benzaldehyde and the *Mannich reaction* ($HCHO+R_2NH$) has also been used in some cases. This is the system which has been used in the excellent definitive, accounts of pyrimidine chemistry by *D.J. Brown*.

The compounds were screend for antibactirial activity using cup - platr method 4 at a concentration if 5 mg ml-1 against *S.aureus* and *E.Coli* compounds 2,3,4 and 5 were found inactive against both the organism. Other compounds showed a moderate or weak activity against *S .aureus* compounds 1,6,7,showed a very strong inhibition and other showed a very strong inhibition and other showed a medium activity *E.Coli.*

TP106

BENIGN APPROACHES FOR THE SYNTHESIS OF 2,4,6-TRIARYLPYRIDINES AND THEIR 1,5-DIKETONE INTERMEDIATES

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Since Krohnke's original report on the synthesis of 2,4,6-triarylpyridines, there has been a plethora of research targeting their syntheses.[1] Nevertheless there are no reported simple 'one-pot' procedures for the synthesis of amino functionalised compounds, for example, 4'-aryl-2,6-bis(4-aminophenyl)pyridines (Fig 1). We have deemed these compounds as precursors for further elaboration en route to the synthesis of DNA binding ligands, in particular targeting G-quadruplex DNA which has recently received much attention as a possible target in cancer therapy.[2]

We recently reported the efficient 'one-pot' synthesis of 4'-(pyridyl)-terpyridines in polyethylene glycol (PEG)[3] and herein we report the 'one-pot' synthesis of 4'-aryl-2,6-bis(4-aminophenyl)pyridines and their corresponding 1,5-diketone intermediates in PEG with high yield, purity and negligible waste. This 'one-pot' base catalysed approach in making amino-substituted pyridines of this type is without precedent.

Process intensification is another tool for green chemistry.[4] It has been developed in the present study to prepare the intermediate 1,5-diketones in a single pass on a spinning disc processor (SDP) in high yield (Fig 2). This is associated with a residence time of ca 0.5 secs, whereas some reactions using traditional batch technology take several hours to go to completion.

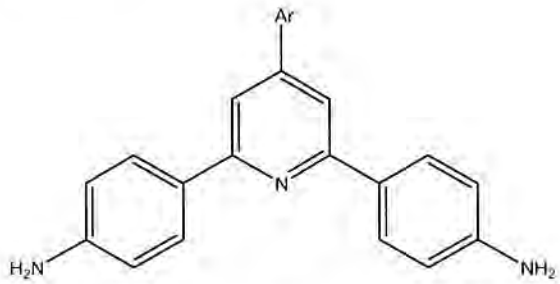

Fig 1 4'-aryl-2,6-bis(4-aminophenyl)pyridines

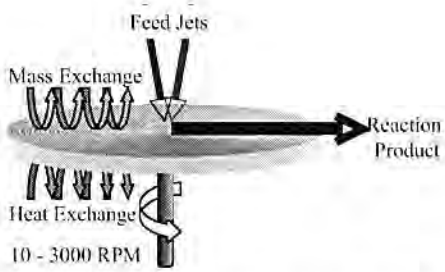

Fig 2 Spinning Disc Processor (SDP)

References:

1. Cave, G.W.V., Raston, C.L., *J. Chem. Soc., Perkin Trans 1.*, 2001, 1, 3258; Cave, G.W.V., Raston, C.L., *Chem. Commun.*, 2000, 2199; Rothenberg, G, Downie, A.P., Raston, C.L., Scott, J.L., *J. Am. Chem. Soc.*, 2001, 123, 8701.
2. Kelland, L.R., *Eur. J. Cancer.*, 2005, 41, 971; Dexheimer, T.S., Sun, D, Hurley, L.H., *J. Am. Chem. Soc.*, 2006, 128, 5404.
3. Smith, C.B., Raston, C.L., Sobolev, A.N., *Green Chem.*, 2005, 7, 650.
4. Anantachoke, N, Makha, M, Raston, C.L., Reutrakul, V, Smith, N.C., *J. Am. Chem. Soc.*, 2006, 128, 13847-13853.

TP108

SYNTHESIS OF NEW HETEROCYCLIC STRUCTURES BASED ON INDOLES

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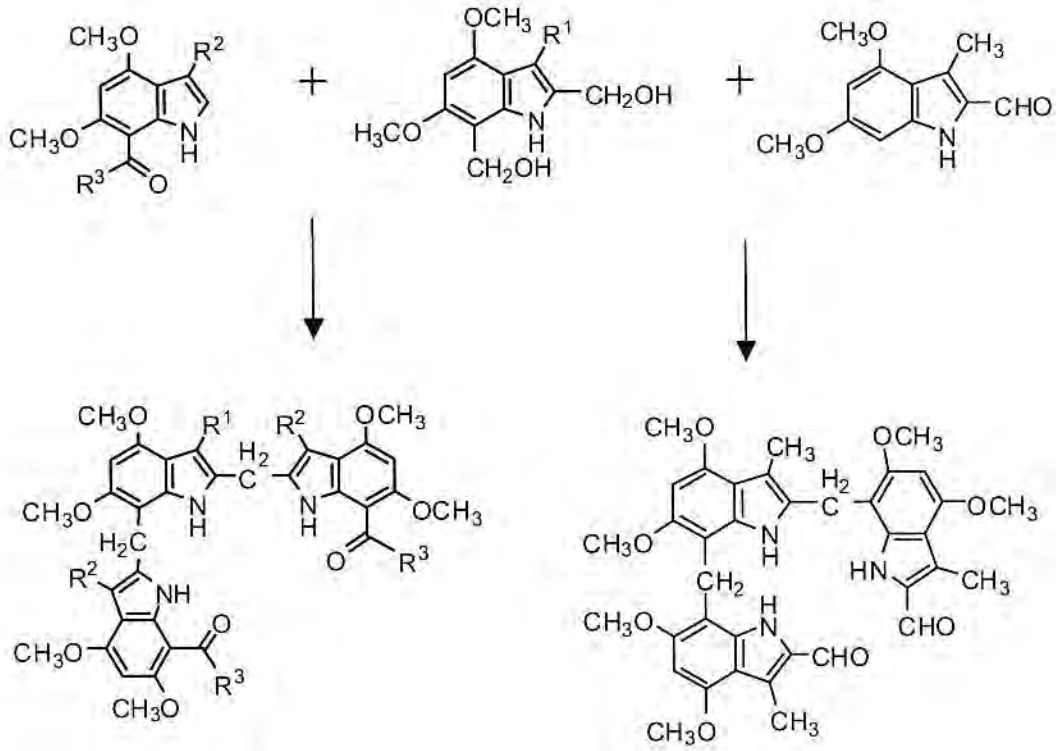
Electrophilic substitution reactions of 3-substituted 4,6-dimethoxyindole-2,6-dimethanols and 3-substituted 4,6-dimethoxyindole-7 and 2-carbaldehyde afforded triindolyl dialdehydes. The variation of substituents at C-7 of indole-7-aldehydes and at C-2 of indole-2-aldehydes has also been investigated.



TP109

TOWARDS THE SYNTHESIS OF DIMERIC PYRANONAPHTHOQUINONES USING A DOUBLE HAUSER ANNULATION STRATEGY

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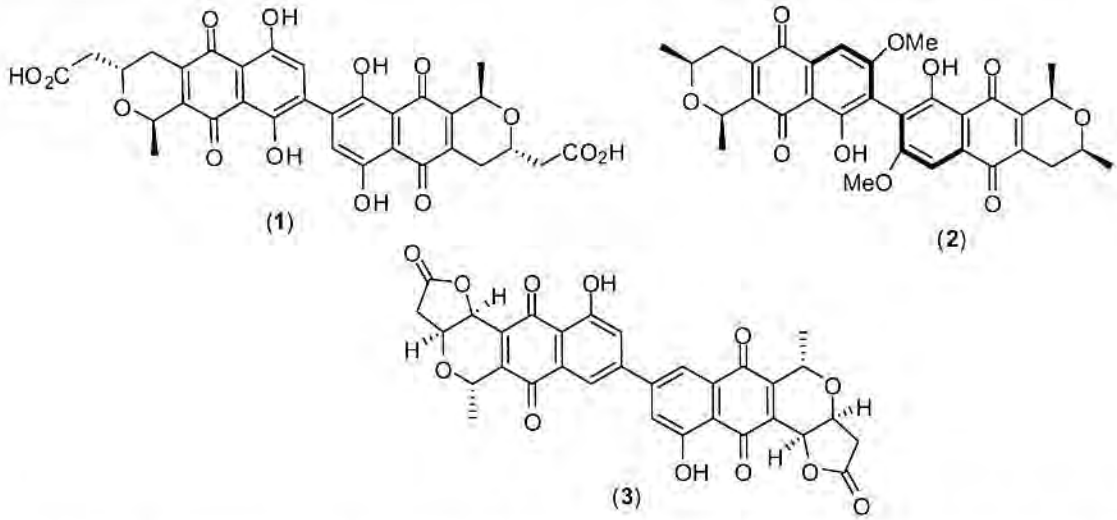
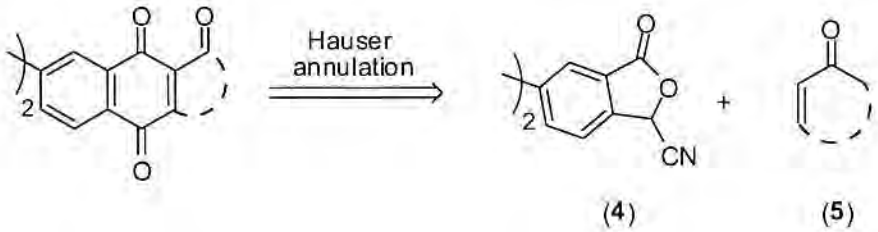
Pyranonaphthoquinone antibiotics have attracted interest due to their inhibitory activity against a variety of pathogenic fungi, yeast and gram-positive bacteria.[1] Three dimeric naphthoquinones of this class include actinorhodin (1), isolated from the actinomycete *Steptomyces coelicolor*,[2] cardinalin C3 (2), discovered in the New Zealand toadstool *Dermoycbe cardinalis*[3] and crisamicin A (3), isolated from the microorganism *Micronospora purpureochromogenes*.[4]



Our generic proposal for the synthesis of dimeric pyranonaphthoquinone antibiotics is based around a double Hauser annulation[5] of bis-phthalides (4) with enones (5). In this fashion, the pyranonaphthoquinone backbone could be constructed in a one pot protocol. In order to test the viability of this approach, various bis-phthalides are being used in the double annulation reaction.



References:

1. Brimble MA, Nairn MR, Duncalf LJ. *Nat. Prod.Rep*, 1999, 16 (3), 267-281.
2. Brockmann H, Pini H. *Naturwissenschaften*, 1947, 34, 190; Brockmann H, Pini H, Plotho, O. *Chem. Ber.* 1950, 83, 161.
3. Buchanan MS, Gil M, Yu JJ. *J. Chem. Soc. Perkin Trans 1*, 1997 (6), 919-925.
4. Nelson R, Pope JA Jr, Luedemann GM, McDaniel LE, Schaffner, CP. *J. Antibiot.* 1986, 39 (3), 335-344; Ling D, Shield LS, Rinehart KL Jr. J Antibiot. 1986, 39 (3), 345-333.
5. Hauser FM, Rhee RP, *J. Org Chem*, 1978, (43), 178-180.

TP110

THE SYNTHESIS OF NOVEL BLOCKED DIHYDROPTERINS AND THE ACTIVATION OF NITRIC OXIDE SYNTHASE

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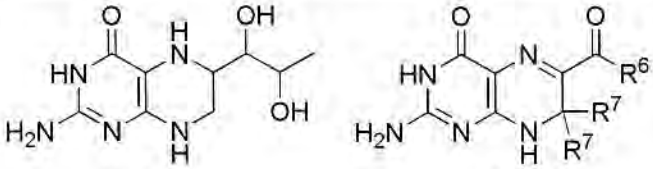
Tetrahydrobiopterin (1) is the cofactor for the nitric oxide synthases (NOS) in which it plays a role as both a structure forming agent in the dimeric active protein and importantly as a one electron reductant in the oxidation cycle [1]. Whilst many inibitors of nitric oxide synthases are known, very few compounds have been found to be activators; such compounds could be important in the therapy of cardiovascular disease in which the supply of NO is insufficient to maintain proper arterial function. A few years ago, we showed that blocked dihydropterins such as 2 are effective in cell and tissue based assays for NO production [2]. Notably, compounds such as 2 are highly oxidatively stable in contrast to tetrahydrobiopterin, which is potentially a major advantage in therapeutic applications. In order to exploit these discoveries therefore, it is important understand the mechanism by which these compounds act and to have a synthetic methodology that enables the synthesis of a wide variety of analogues of 2. This paper will present data dealing with each point.



1 2

In principle, blocked dihydropterins themselves could support NOS activity by being reduced at the enzyme's active site and subsequently transferring an electron to the Fe-heme. Although blocked dihydropterins do undergo one reversible one-electron oxidation and reduction as shown by electrochemical measurements [3], we have found no evidence that they are able directly to support NO production by NOS. On the other hand, chemically synthesised blocked tetrahydropterins do support NO production. For this to be a competent biological mechanism, reduction must therefore occur within the cell and we have also shown that many blocked dihydropterins are substrates for dihydrofolate reductase.
Our new synthesis of blocked dihydropterins centres on the challenge of producing a library of compounds with a wide range of substituents on C6 and C7, including potentially the need for stereoisomerically pure compounds at C7. After much experimentation, we have developed a high yielding route from simple α-aminoacids using Weinreb amide chemistry for the insertion of the C6 substituent together with selective alkylation of a 4-bromophenylimine to insert the second C7 substituent.

1 Wei C-C, Crane BR, Stuehr DJ, *Chem. Rev.* 2003: 103, 2365-2383.
2. Kununthur SR, Suckling CJ, Gibson CL, Wadsworth RM. *Pteridines*, 2005: 16, 112.
3. Suckling CJ, Huggan JK, Berlouis LEA, Gibson CL. *Pteridines*, 2005: 16, 112.

TP111

DIVERSIFIABLE SYNTHESES OF PYRROLO[2,3-*d*]PYRIMIDINES AND PYRIMIDO[2,3-*d*]PYRIMIDINES: THE MICHAEL AND CLAISEN ROUTES

Colin J Suckling, Colin L Gibson, Judith K Huggan, Jonathan Adcock, and Jeong-Hwan Lee

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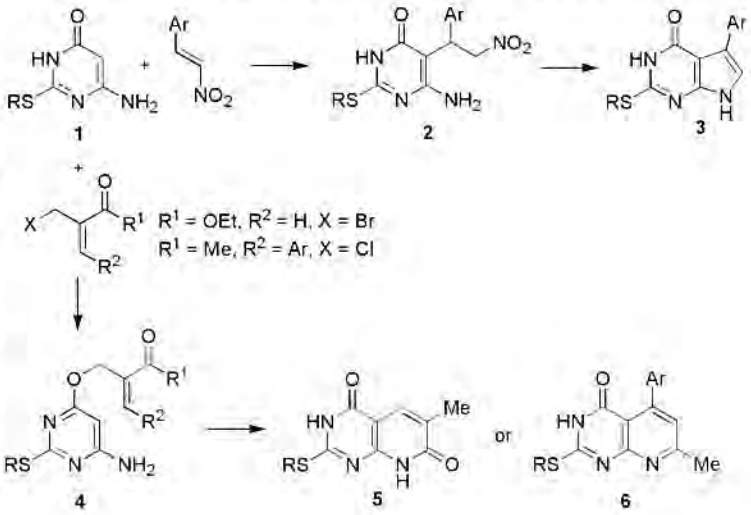
Analogues of folic acid and its biosynthetic precursors have been of interest for their biological activity for many years especially in anticancer and antibacterial fields. Whilst the synthesis of fused pyrimidines with 2-amino substituents has been well established for many years, divergent synthetic routes capable of providing diverse substitution throughout the target molecules including C2 have not been extensively described. In previous work, we have shown how 2-alkylthio groups can be used as late stage sites for diversification by nucleophilic substitution in the related compounds, pteridines [1,2]. These routes involve the 5-nitrosation of 2-alkylthiopyrimidines, which is a high yielding reaction. In contrast, the formation of new carbon-carbon bonds at C5 in 2-alkylthiopyrimidines is a low yielding reaction, presumably because of the poorer electron donating power of the alkylthio group compared with the amino group. This paper will describe two general methods of obtaining the target fused pyrimidines and their elaboration into compounds with a variety of C2 substituents.

In the first method, we have extended the synthesis using nitroalkenes as electrophiles described by Taylor for the anticancer drug, Alimta [3]. In outline, the 2-benzylthiomethylpyrimidine 1 reacted with a range of nitrostyrenes to afford the Michael adducts 2 which were cyclised to the pyrrolo[2,3-*d*]pyrimidines 3 using a variety of reagents. In the second and novel method, α-halomethyl-α,β-unsaturated carbonyl compounds reacted with 1 in the presence of a mild base to form the 4-ether 4, which was not always isolable. Under thermal conditions with or without titanium(IV) chloride catalysis, Claisen rearrangement took place affording the C5 alkylated pyrimidine which, if a ketone, underwent concomitant cyclisation to afford the pyrimido[2,3-*d*]pyrimidines 5 or if an ester, was cyclised in a subsequent step using TMD to afford 6. The final substitution of the alkylthio group by an amino nucleophile was found to be very sensitive to the structure of the substrate and to the reaction conditions (thermal or microwave) and the results shed light on the requirements for successful substitution using microwave radiation.



1. Guiney D, Gibson CL, Suckling CJ. *Org.Biomol.Chem.*, 2003: 1, 664-675.
2. Gibson, CL, La Rosa S, Suckling CJ. *Org.Biomol.Chem.*, 2003: 1, 1909-1918.
3. Taylor EC, Liu B. *J. Org. Chem.*, 2003: 68; 9938-9947

TP112

1,9-BRIDGED THIANTHRENE AND RELATED DERIVATIVES FOR DEVELOPING NEW FUNCTIONAL MOLECULES

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It has been known that thianthrene deirivatives are folded along the S-S axis, and exist as "butterfly structures" in the equilibrium state of two "flip-flap" conformational isomers. As a basic study to develop new sort of functional molecules regulating the thianthrene flip-flap motion, the authors have demonstrated the great influence by peri substituent(s) on the sterochemical change of 10-*S*-monoxythianthrene-5-*S*-substituted sulfilimine derivatives.[1] To extend the study to more rigid system several 1,9- bridged thianthrene derivatives have been synthesized and their chemical properties and behabior have been studied.

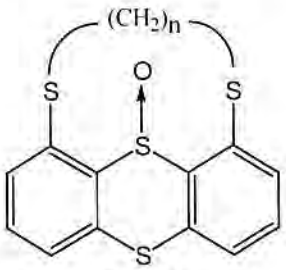

Figure 1. 1,9-bridged thianthrene derivative

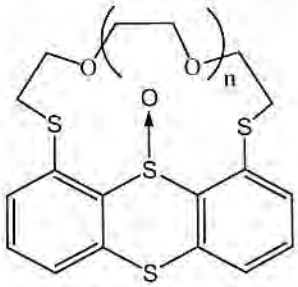

Figure2. Polyether thianthrene derivative

The detail of the chemical properties and behabior together with their related derivatives will be presented including X-ray crystallographic analyses of several key compounds.

[1] Morita, H; Kawaguchi, H. *Chem. Eur. J.* 2000, *6*, 3976.

TP113

APPLICATION OF THE BETTI REACTION FOR THE SYNTHESIS OF NEW CHIRAL LIGANDS

István Szatmári, Ferenc Fülöp

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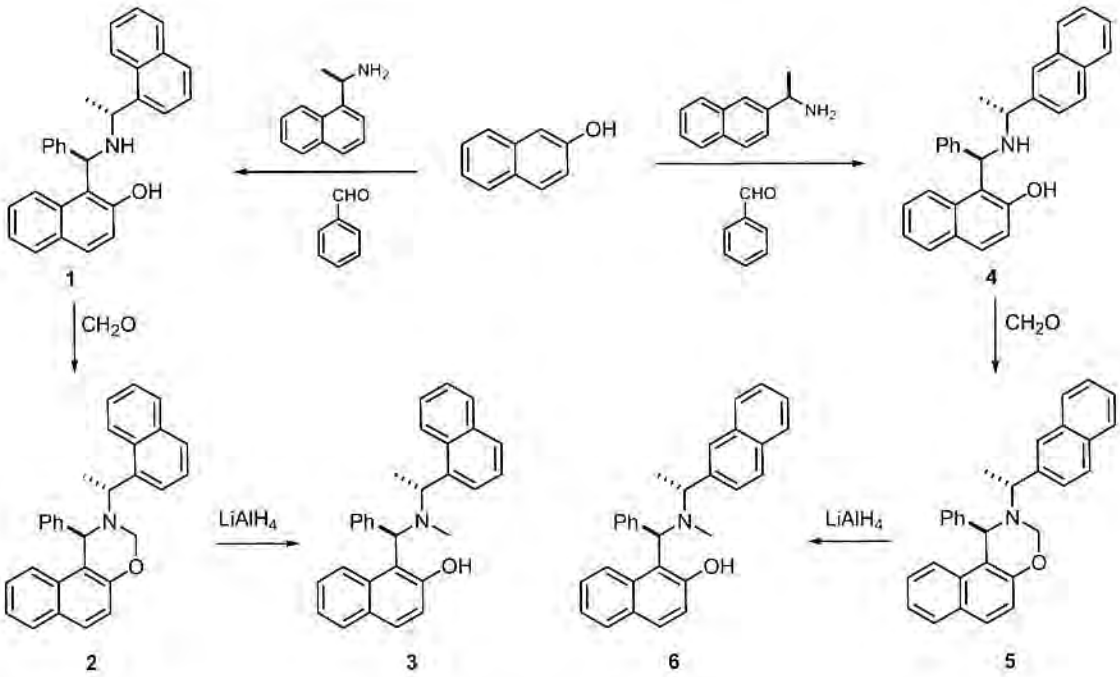
One of the most important applications of the three-component Betti reaction is in solvent-free reactions where ammonia has been replaced by chiral amines. Nonracemic *N*-substituted Betti base derivatives obtained in this way have been used successfully as chiral ligands in the benzaldehyde diethylzinc addition.[1,2]



Starting from (*R*)-(+)-1-(1-naphthyl)ethylamine and (*R*)-(+)-1-(2-naphthyl)ethylamine, respectively, new enantiopure aminonaphthols 1 and 4 were prepared. From 1 and 4 via oxazines 2 and 5, followed by reductive ring opening, the *N*-methyl derivatives 3 and 4 were also prepared. By using the aminonaphthols 1, 3, 4 and 6 as chiral ligands in benzaldehyde diethylzinc addition, depending on the reaction conditions, the ee values of the main enantiomer could be shifted up to 98%.

References:
[1] Szatmári I.; Fülöp F. *Curr. Org. Synth.* 2004, 1, 155-165.
[2] Ji J.-X.; Wu J.; Au-Yeung T. T.-L.; Yip C.-W.; Haynes R. K.; Chan A. S. C. *J. Org. Chem.* 2005, 70, 1093-1095.

TP114

ONE-POT SYNTHESIS OF *MESO*-FORMYL-SUBSTITUTED FREE BASE PORPHYRINS VIA S_NAR REACTIONS WITH (TRIALKYLSILYL)METHYLLITHIUM REAGENTS

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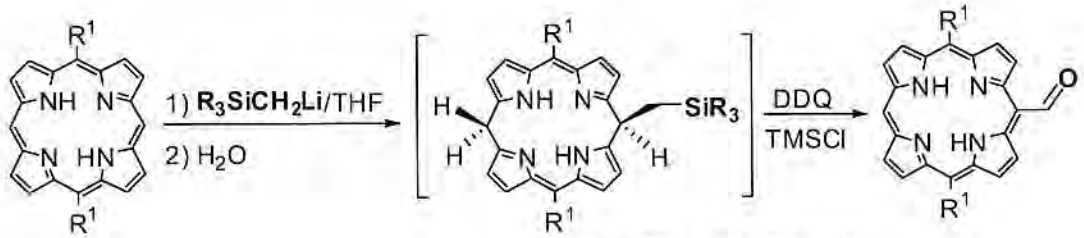
Porhyrins and metalloporphyrins have been investigated for many years in detail because of their wide application fields, including catalysis, medicine, and materials. It has also been well documented that the physical, chemical, and biological properties of porphyrins can systematically be regulated through proper functionalization of the porphyrin core. In this context, impressive progress has recently been made in the development of new synthetic strategies and intermediates for the synthesis of porphyrin derivatives bearing a diverse variety of peripheral substituents.[1] Formylporphyrins are one of the most useful precursors for subsequent transformations to synthesize more complicated porphyrin derivatives. Only a few methods, however, have been available for the introduction of formyl group to the porphyrin core.[2]

In this paper, we report a novel and simple one-pot access to *meso*-formylporphyrins that can easily be achieved by the nucleophilic addition of (trialkylsilyl)methyllithium reagents to 5,15-diaryl and 5,15-dialkyl-substituted free base porphyrins followed by hydrolysis with water and oxidation with DDQ in the presence of TMSCl.



R^1 = Ph, 4-$CH_3C_6H_4$, ^{i}Bu, etc.

R_3SiCH_2Li = Me_3SiCH_2Li, $PyMe_2SiCH_2Li$

References:

(1) We have developed several functionalization reactions of porpyrins: (a) Takanami, T.; Hayashi, M.; Chijimatsu, H.; Inoue, W.; Suda, K. *Org. Lett.* 2005, *7*, 3937–3940. (b) Takanami, T.; Hayashi, M.; Hino, F.; Suda, K. *Tetrahedron Lett.* 2003, *44*, 7353–7357.

(2) Senge, M. O.; Hatscher, S. S.; Wiehe, A.; Dahms, K.; Kelling, A. *J. Am. Chem. Soc.* 2004, *126*, 13634–13635.

TP115

TOTAL SYNTHESIS OF STEMONAMIDE AND RELATED ALKALOIDS USING RADICAL CASCADE

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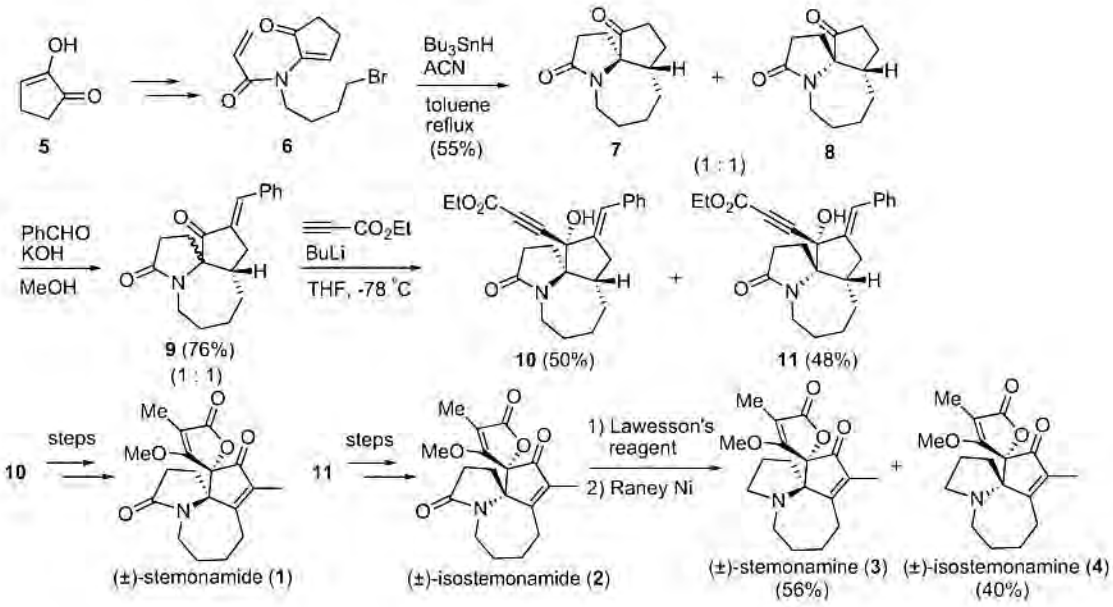
Division of Pharmaceutical Sciences, Graduate School of Natural Science and Technology, Kanazawa University

Stemonamide (1), isostemonamide (2), stemonamine (3) and isostemonamine (4) were isolated from the roots of *Stemona japonica*, which have been used as Chinese and Japanese folk medicine.[1] The complex tetracyclic structure with two spirocyclic systems make these compounds attractive targets for synthesis. Previously, we reported the regioselective radical cyclization onto enamides and its application to radical cascade.[2] Herein we report the synthesis of stemonamide and related alkaloids based on the radical cascade as a key step. Radical precursor 6 was readily prepared from 1,2-cyclopentanedione 5. Treatment of 6 with Bu_3SnH/ACN (1,1-azobiscyclohexanecarbonitrile) caused radical cascade involving 7-*endo-trig*/5-*endo-trig* cyclization to afford the mixture of tricyclic compounds 7 and 8 (1:1). The mixture of tricyclic compounds 7 and 8 was converted to α,β-nusaturated ketones 9 as the by aldol condensation with benzaldehyde. Addition of lithium ethyl propiolate to α,β-nusaturated ketones 9 afforded compounds 10 and 11 in 50% and 48% yields, respectively. Synthesis of stemonamide (1) and isostemonamide (2) was accomplished by elaboration of compounds 10 and 11 including construction of methyl tetronate moiety, oxidative cleavage of olefin, and introductions of the methyl group and double bond, respectively. Stemonamine (3) and isostemonamine (4) were synthesized from isostemonamide (2) by selective reduction of lactam via thioamidation.



References:

(1) Ye, Y.; Qin, G.-W.; Xu, R.-S. *J. Nat. Prod.* 1994, *57*, 665-669.

(2) (a) Ishibashi, H.; Kato, I.; Takeda, Y.; Kogure, M.; Tamura, O. *Chem. Commun.* 2000, 1527-1528. (b) Taniguchi, T.; Ishita, A.; Uchiyama, M.; Tamura, O.; Muraoka, O.; Tanabe, G.; Ishibashi, H. *J. Org. Chem.* 2005, *70*, 1922-1925. (c) Taniguchi, T.; Tamura, O.; Uchiyama, M.; Muraoka, O.; Tanabe, G.; Ishibashi, H. *Synlett* 2005, 1179-1181.

TP116

PHOTOCHEMICAL REACTIONS OF 1-ALKYL-7-AZAISATINS WITH 2,3-DIMETHYLBUT-2-ENE

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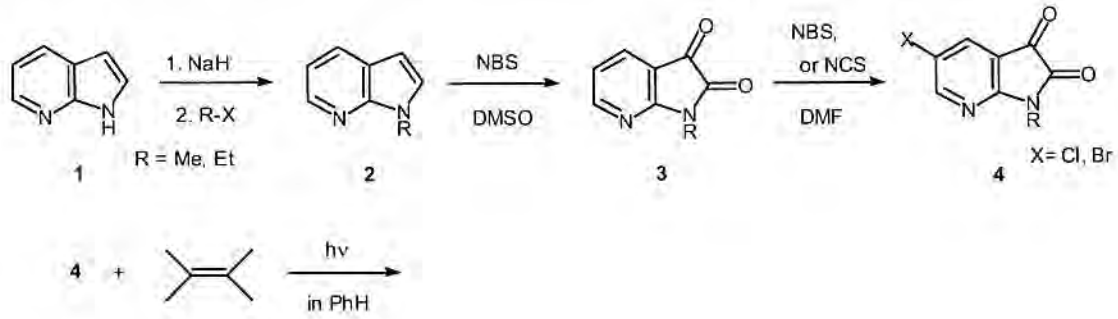
During our studies on photochemical reactions of cyclic vicinal polycarbonyl compounds,[1] we need to prepared 1-alkyl-7-azaisatins (3) and 1-alkyl-5-halo-7-azaisatins (4). The compounds 3 were prepared from commercially available 7-azaindole (1) via 1-alkyl-7azaindoles (2), then halogenation of 3 with NBS or NCS in DMF under mild conditions. In order to clarify the photochemical intrinsic behaviour of heterocyclic vicinal dicarbonyl compounds, we have examined the photochemical reactions of 3 and 4 with 2,3-dimethylbut-2-ene in degassed benzene. The photoreactions of 3 with the alkene gave the corresponding adducts as products of Paterno Büchi reaction in moderate yields. On the other hand, the photochemical reactions of 4 afforded photoproducts in good yields.



References:
1. a) Tatsugi J, Hara T, and Izawa Y, *Chem. Lett.*, 1997; 177-178. b) Tatsugi J, Ikuma K, and Izawa Y, *Heterocycles*, 1996; 43, 7-10. c) Tatsugi J, Ikuma K, and Izawa Y, *Tetrahedron Lett.*, 1995; 47, 8611-8612.

TP117

MODIFICATION OF ISOQUINOLINE ALKALOID NOSCAPINE VIA SUZUKI COUPLING

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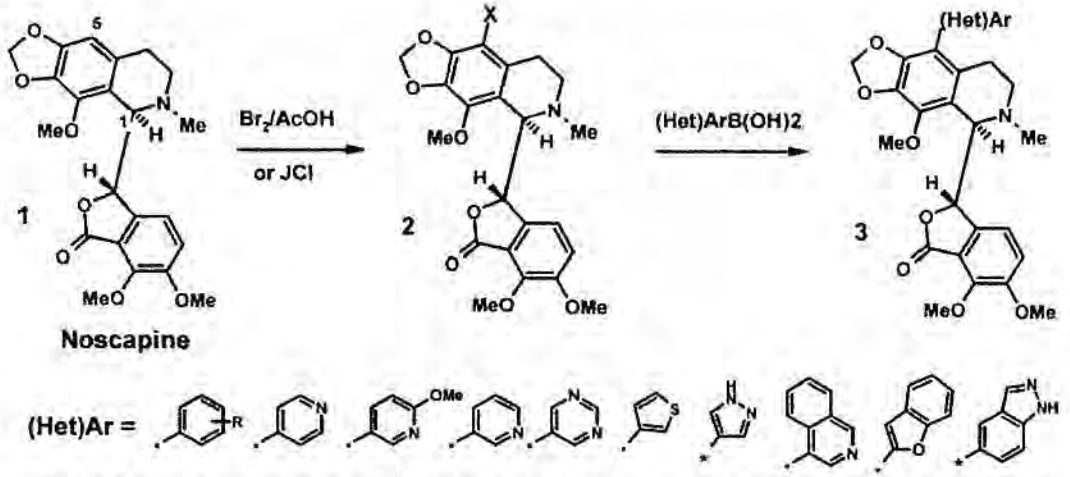
Noscapine (1), alkaloid from *Papaver somniferum L. Papaveraceae* widely used as an oral cough suppressant with no known toxic side effects, has attracted a great deal of attention in past decade because of discovered its anti-cancer activity. However, there are only limited data about noscapine and its derivatives reactions with preservation of the original core and stereochemistry.



R= H, 4-MeO, 3- and 4-OH, 3- and 4-COOH, 3- and 4-CONH$_2$, 3- and 4-NHCONHPh, 4-SO$_2$Me, 3-NMe$_2$.

Here we report the synthetic approach to 5-aryl(hetaryl)-substituted noscapine derivatives 3. The developed synthetic sequence utilize a palladium catalysed Suzuki coupling of 5-bromo- or 5-iodonoscapines 2 and a wide range of boronic acids bearing either electron donating or electron withdrawing groups. This approach provides us with desired optically pure materials in a good yield. All final compounds were obtained as pharmaceutically acceptable hydrochlorides.

A biological activity of the resultant compounds was profiled using a panel of human tumor cell lines, DLD-1 (colorectal adenocarcinoma), DU-145 (metastatic hormone-refractive prostate cancer), T-47D (metastatic breast cancer), and Jurkat T cells (leukaemia). The derivatives were shown to have different levels of cell specificity profiles in the cytotoxicity assays. Two synthetic analogues were also shown to induce apoptosis in Jurkat T cells and possess an anti-mitotic activity as evident from the data obtained on a panel of the human cancer cells

TP118

STEREOCHEMISTRY OF THE UGI-TYPE MCR OF NOVEL PROLINE-BASED ALDEHYDO-ACIDS.

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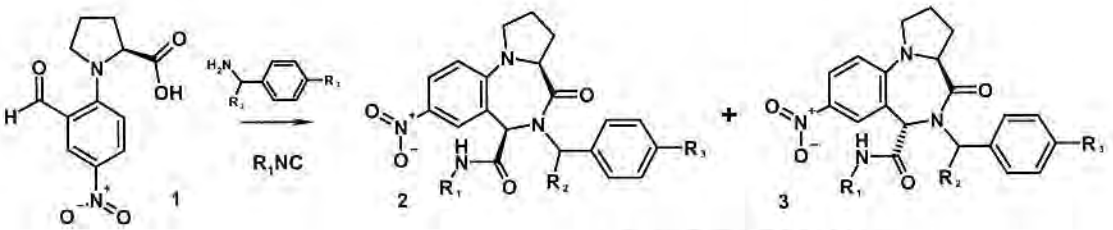
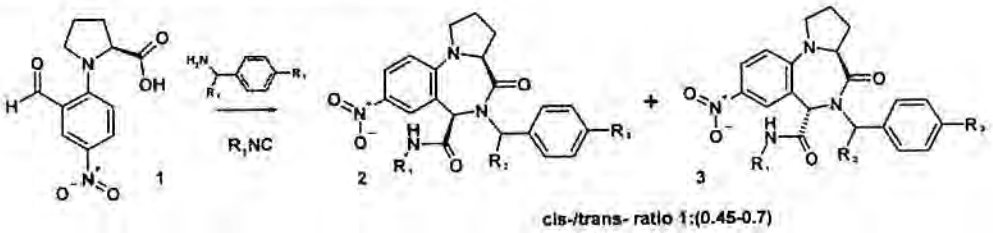
[b] *Chemical Diversity Research Institute, Khimki, Moscow Reg. 114401, Russia*

The Ugi-type multicomponent reaction (U-MCR) is well known and a widely employed tool for the synthesis of peptidomimetics, which are attractive objects for the medicinal chemistry investigations. Because of formation of a new stereogenic center during U-MCRs, considerable efforts to control its stereochemistry have been made by numerous researchers. Different chiral auxiliaries have been used; however, only chiral amines have resulted in an acceptable degree of diastereoselectivity. In this case, the reaction conditions and concentrations of educts can strongly interfere with the course of condensation, and it was therefore assumed that different reaction conditions of the U-4MCRs can lead to quite different types of reaction mechanisms.
An important version of U-MCR is the intramolecular four-center-three-component reaction (U-4C-3CR) where two of the four functional groups belong to one molecule. At the same time, only limited data on stereochemical behavior of keto- acids in Ugi-like 4C-3CR have been reported so far. The stereochemistry of U-4C-3CRs with aldehydo-acids was not studied at all.



Only (3*a*S,6R)-**2** and (3*a*S,6S)-**3** are shown; (3*a*R,6S)-**2** and (3*a*R,6R)-**3** as well as racemic mixtures **2** and **3** were synthesized from (R)- and (R,S)-**1**

Here we report design and synthesis of new enantiopure proline-based aldehydo- acids 1 with the purpose of investigating their reactivity in an intramolecular Ugi-type multicomponent reaction. Several optically pure derivatives of 5-*N*-substituted 8-nitro-4-oxo-2,3,3a,4,5,6-hexahydro-1*H*-pyrrolo[1,2-*a*][1,4]benzodiazepine-6-carboxamides have been obtained during the course of this work and their structures have been determined using NOESY NMR experiments and single crystal X-ray analysis. The effect of reaction conditions and chirality of reaction components on the observed stereochemical outcome has been examined and mechanistic explanation has been proposed.



Only (3*a*S,6R)-**2** and (3*a*S,6S)-**3** are shown; (3*a*R,6S)-**2** and (3*a*R,6R)-**3** as well as racemic mixtures **2** and **3** were synthesized from (R)- and (R,S)-**1**

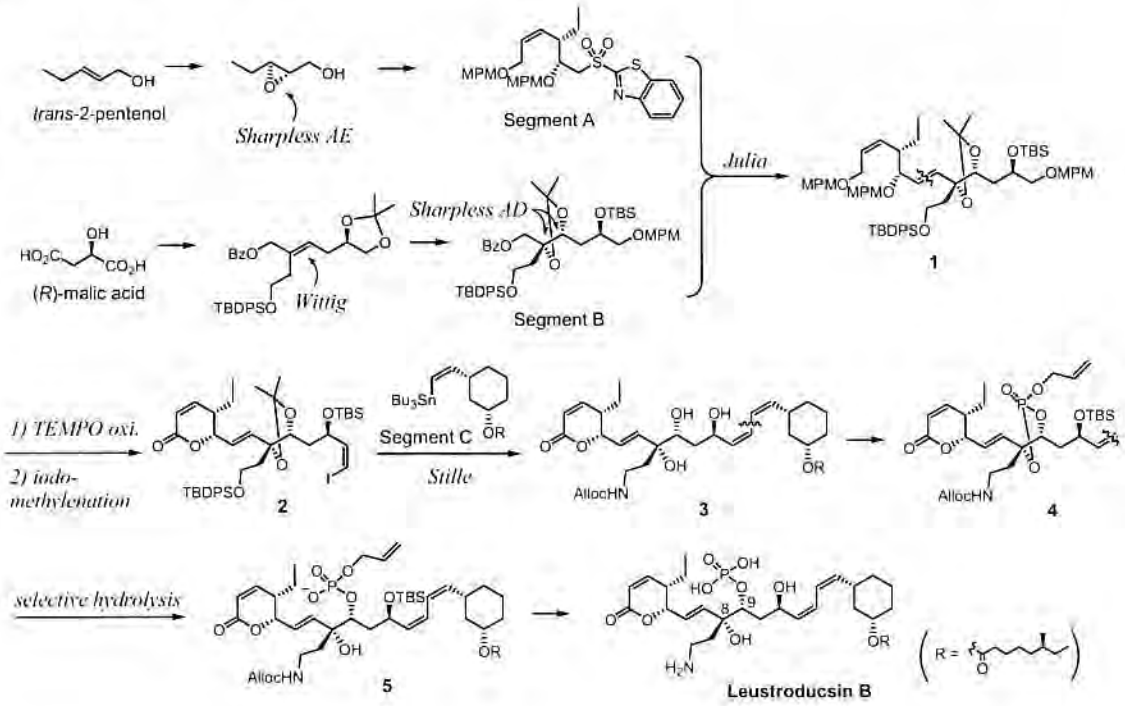
TP119

HIGHLY CONVERGENT TOTAL SYNTHESIS OF LEUSTRODUCSIN B

Tomoyuki Tsunemi,[1] Takafumi Hosokawa,[1] Masahiro Ikejiri,[1] Kazuyuki Miyashita[1,2] and Takeshi Imanishi[1]

[1] *Graduate School of Pharmaceutical Sciences, Osaka University*
[2] *Faculty of Pharmacy, Osaka Ohtani University*

Leustroducsin B, a metabolite of *Streptomyces platensis* SANK 60191, exhibits a variety of interesting biological activities such as induction of a colony-stimulating factor *via* NF-κB activation and thrombopoiesis. We planned to synthesize leustroducsin B by taking a highly convergent route, in which the molecule was divided into three segments A, B and C.
Segment A having a benzothiazolesulfonyl group was synthesized from *trans*-2-pentenol *via* a Sharpless asymmetric epoxidation reaction and ring opening reaction. Segment B was synthesized from (*R*)-malic acid with a highly stereochemical control at the C-8 and C-9 positions by a combination of Wittig reaction and Sharpless asymmetric dihydroxylation. Julia coupling reaction of the segment A with the segment B provided the product 1. α,β-Unsaturated lactone ring formation by TEMPO oxidation and iodomethylenation was successfully achieved to afford 2. Stille coupling reaction of 2 with the segment C, which was prepared by means of asymmetric Diels-Alder reaction, gave the product 3. Formation of a cyclic phosphate from 3 by the original method developed at the total synthesis of fostriecin[1)] gave 4, and subsequent regioselective hydrolysis afforded 5. Finally, removal of protecting groups furnished leustroducsin B successfully.



References:
1) Miyashita K., Ikejiri M., Kawasaki H., Maemura S. and Imanishi T. *J. Am. Chem. Soc.*, 2003; 125, 8238-8243.

TP120

NOVEL PREPARATION OF FLUORINATED ISOINDOLES

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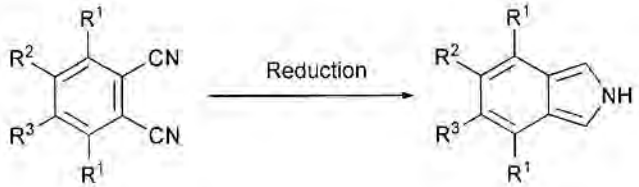
2*H*-Isoindole is a very important, though rather unstable, 10π aromatic heterocycle and has attracted much attention from synthetic and theoretical chemists. Since the aromaticity index (I_A = 150) of isoindole is larger than that of indole (I_A = 146),[1] the instability of isoindole is not due to aromaticity, but attributable to the high HOMO level and existence of an equilibrium between 1*H*-isoindole (isoindolenine).[1] The parent isoindole was successfully prepared by flash vapour pyrolysis (600 °C) of the corresponding retro-Diels-Alder precursor.[2] Many methods for the preparation of stable, substituted isoindole derivatives were reported so far. Contrarily, successful preparations of 1,2,3-free isoindoles are limited. During our continuous studies for the preparation and application of π-expanded porphyrins,[3] we are interested in the stable isoindoles especially 4,5,6,7-tetrafluoro-2*H*-isoindole, which was used as a building block for organic synthesis.[4] However, the reported preparation method of 4,5,6,7-tetrafluoro-2*H*-isoindole required the multi-step conversion starting from the rather expensive materials such as bromopentafluorobenzene and pentafluorobenzene. We succeeded in preparation of 4,5,6,7-tetrafluoro-2*H*-isoindole from 3,4,5,6-tetrafluorophthalo-nitrile in one step.



1a: $R^1 = R^2 = R^3 = F$
1b: $R^1 = F$, $R^2 = R^3 = OC_6F_5$
1c: $R^1 = R^2 = F$, $R^3 = Cl$
1d: $R^1 = R^2 = R^3 = Cl$

2a: $R^1 = R^2 = R^3 = F$
2b: $R^1 = F$, $R^2 = R^3 = OC_6F_5$
2c: $R^1 = R^2 = F$, $R^3 = Cl$
2d: $R^1 = R^2 = R^3 = Cl$

Reduction of 3,4,5,6-tetrafluorophthalonitrile (1a) with borane·THF was conducted in toluene at 95 °C and after acidic quenching a black reaction mixture was obtained. From ^{19}F-NMR, only one product existed in the reaction mixture. From the TLC and GC analyses, only one product was found to exist. Chromatographic separation followed by sublimation, however, gave 4,5,6,7-tetrafluoro-2*H*-isoindole (2a) in rather low yield (37%) as colourless crystals. The bad material balance was due to formation of insoluble products during and after the reaction.

Improvement of the efficiency by changing the reduction conditions as well as the work-up methods are underway and the results involving the reactions with pentafluorophenoxy- and chloro-substituted derivatives will be discussed.

References:

1 Bird, C. W. *Tetrahedron*, 1992, *58*, 335-340.
2 Bornstein, J.; Remy, D. E.; Shield, J. E. *J. Chem. Soc., Chem. Commun.*, 1972, 1149-1150.
3 For a recent report, see: Uno, H.; Nakamoto, K.; Kuroki, K.; Ono, N. *Chem. Eur. J.*, 2007, in press.
4 Warrener, R. N.; Butler, D. N. *Aldrichim. Acta*, 1997, *30*, 119-129.

TP121

RAPID MICROWAVE-ASSISTED PALLADIUM CATALYZED AMINATION, USING COUPLING PARTNERS CONTAINING SENSITIVE FUNCTIONAL GROUPS, BASED ON A TOLUENE / Aq. KOH TWO PHASE SYSTEM.

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Recently, our laboratory developed a microwave-assisted Pd-catalyzed amination protocol for (hetero)aryl bromides and chlorides using a strong base (NaO*t*Bu) and toluene as the solvent.[1] A catalyst loading of only 1 mol% and a temperature of 150°C allows full conversion of substrate in a reaction time of 10 minutes. A great disadvantage of strong nucleophilic bases such as NaO*t*Bu is the limited functional group compatibility on the coupling partners. Therefore, we searched for a fast microwave amination protocol that allows the presence of functional groups that are sensitive towards nucleophilic attack. Since functional group compatibility normally requires the use of a weaker (non-nucleophilic) base and the use of stronger bases is known to give faster amination reactions, we looked at the possibility to use a two phase system of aqueous concentrated KOH / toluene. We reasoned that if the solubility of aqueous KOH in toluene is minimal at the temperature of the reaction, hydrolysis of functional groups which are sensitive towards nucleophilic attack should be avoidable although a strong nucleophilic base is used. Based on our earlier observation that deprotonation of Pd(II)amine complexes can be performed via a solid (base) - liquid interphase mechanism, we believed that a liquid - liquid interphase deprotonation mechanism should be feasible.[2] Alternatively, it is also possible that the small concentration of hydroxide present in the toluene phase performs the deprotonation, while this concentration is inefficient to allow hydrolysis. Our research led to the development of the first microwave protocol which allows the rapid (30 minutes) Pd-catalyzed amination of aliphatic amines with chlorobenzenes, containing sensitive functional groups. This protocol also works for amination reactions on halogenated heterocycles containing sensitive functional groups on the coupling partners.

References:
[1] a) Maes BUW.; Loones KTJ.; Lemière GLF.; Dommisse RA. *Synlett*, 2003, 1822-1825 b) Maes BUW.; Loones KTJ.; Hostyn S.; Diels G.; Rombouts G. *Tetrahedron*, 2004, 60, 11559-11564.
[2] Meyers C.; Maes BUW.; Loones KTJ.; Bal G.; Lemière GLF.; Dommisse RA. *J. Org. Chem.* 2004, 69, 6010-6017.

TP122

TOTAL SYNTHESIS OF DISCORHABDIN F, PRIANOSIN B AND RELATED OXA ANALOGUES BY DEHYDROGENATION AND DETOSYLATION REACTION

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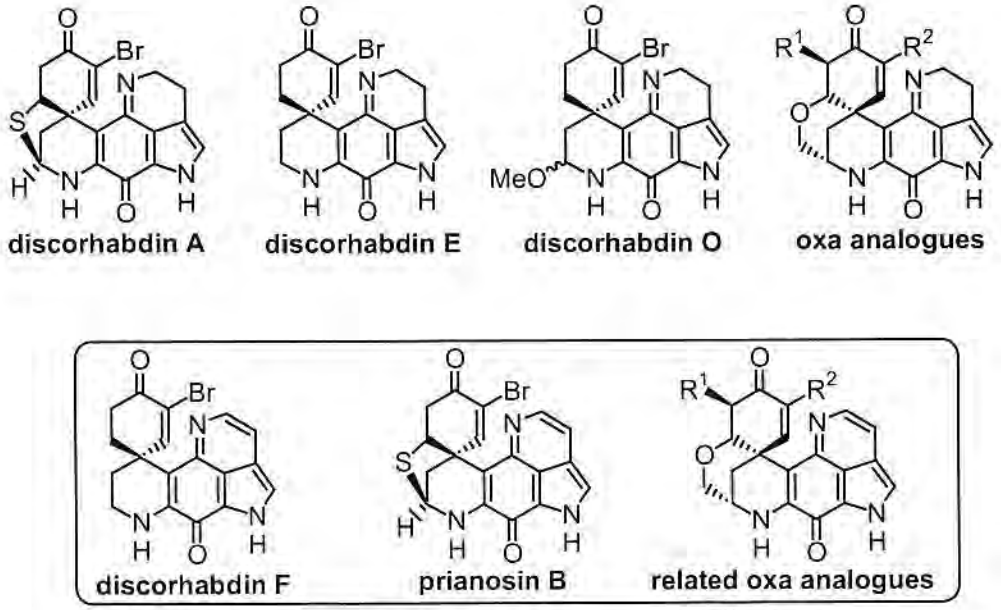
Discorhabdins and prianosins were isolated from marine sponges such as New Zealand sponges of the genus *Latrunculia*, Okinawan sponge *Prianos melanos*, and Fijian sponge *Zyzzya cf.* They have a peculiar structure consisting of both azacarbocyclic spirodienone and pyrroloiminoquinone systems and have attracted much attention as new antitumor lead compounds due to their strong cytotoxicity. Among them, discorhabdin A shows especially potent activity *in vitro*.

We have already achieved the first stereoselective total synthesis of discorhabdin A.[1] Furthermore, by using synthetic intermediate of discorhabdin A, we have synthesized various discorhabdins: discorhabdins E, O and discorhabdin oxa analogues.

Although discorhabdin A shows potent activity, it is unstable. Therefore, we synthesized unnatural oxa analogues of discorhabdin A. Oxa analogues proved to show potent activity *in vitro* similar to that of discorhabdin A.

In this work, we synthesized discorhabdins having a fully unsaturated pyrroloiminoquinone unit and accomplished the synthesis of discorhabdin F, prianosin B and related oxa analogues. The key reaction for them is dehydrogenation and detosylation of pyrroloiminoquinone unit by using a catalytic amount of NaN_3. We will discuss the detail of this detosylation and dehydrogenation reaction.



References:

1) Tohma, H.; Harayama, Y.; Hashizume, M.; Iwata, M.; Kiyono, Y.; Egi, M.; Kita, Y. *J. Am. Chem. Soc.*, 2003; 125, 11235-11240; Harayama, Y.; Yoshida, M.; Kamimura, D.; Wada, Y.; Kita, Y. *Chem. Eur. J.*, 2006; 12, 4893-4899.

TP123

SELF ASSEMBLED MONOLAYER FORMING CAPPED PORPHYRIN

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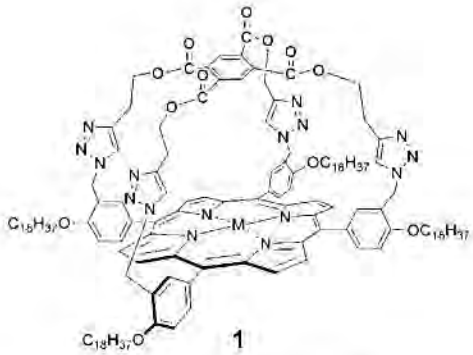
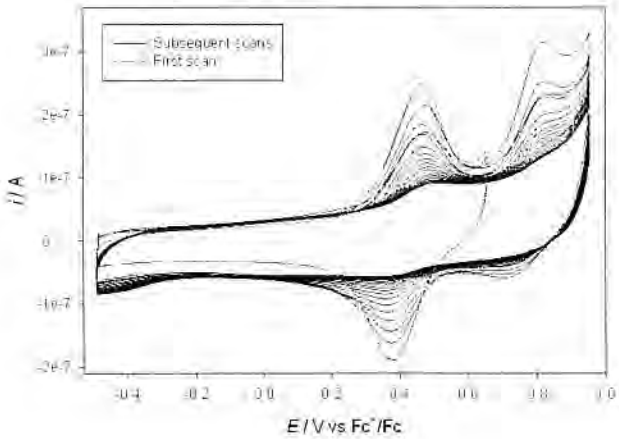
The possibility of self-assembling molecules onto surfaces provides a unique avenue through which one can functionalize materials with complex architecture, dramatically altering the physical and chemical properties of surfaces. Previously atomic force microscopy (AFM) studies have demonstrated that tetra(octadecyloxyphenyl) porphyrins can generate stable monolayers on carbon based surfaces.[1] SAMs have also been observed from di-linked or "strapped" porphyrins [2] providing further evidence that the tetra(octadecyloxyphenyl) porphyrins are prime platforms that allow the creation of various surface architectures.

Here we present the results obtained for a "capped" tetra(octadecyloxyphenyl) porphyrin 1 designed to immobilize readily onto carbon based surfaces. The molecule is synthesised through the application of regioselective copper (I) catalysed "click" chemistry between tetra(*p*-octadecyloxy-*m*-methylazide-phenyl) porphyrin and tetrapropargyl pyromellitate. It has displayed strong adsorption to both glassy carbon and HOPG surfaces and extraordinarily good electrochemical stability. We therefore pursue the possibility of applying the system as an electrochemical porphyrin-based sensor.



1

Degradation of the SAM



References:
1. Otsuki J, Nagamine E, Kondo T, Iwasaki K, Asakawa M and Miyake K. *J. Am. Chem. Soc.* 2005; 127, 10400-10405
2. Ikeda T, Asakawa M, Miyake K and Shimizu T. *Chem. Lett.* 2004; 33, 1418-1419

TP124

SYNTHESIS AND PROPERTIES OF O^6-G-ALKYL-O^6-G INTERSTRAND CROSS-LINKED DNA AS A PROBE TO INVESTIGATE RESISTANCE TO BIFUNCTIONAL ALKYLATING CHEMOTHERAPEUTIC AGENTS

Christopher J. Wilds, Jason D. Booth and Anne M. Noronha

Concordia University, Department of Chemistry & Biochemistry, Montreal, Quebec, Canada.

Therapeutic alkylating agents are among some of the oldest anti-cancer agents. They can be categorized as monofunctional or bifunctional alkylating agents; the latter category includes nitrogen mustards and methyl methane sulfonates[1].The major cytotoxic lesion induced by these agents are interstrand cross-links (ICL), which if left unrepaired, prevent DNA strand separation and normal mitosis. Resistance to the cytotoxic effects produced by these lesions often results from enhanced repair of the damage[2]. Homologous recombination and nucleotide excision have been implicated in cross-link repair in bacteria and mammalian cells, however, elucidation of the exact mechanism(s) involved in these processes is still lacking[3]. Since development of resistance is one of the primary reasons for treatment failure, a better understanding of the processes by which such DNA lesions are recognized and repaired can lead to the development of more effective alkylating agents and treatment regimens.

In order to investigate repair processes, substrates of defined chemical structure are required. Such substrates are challenging to prepare, particularly in the quantities needed to conduct structural and biochemical studies. Our group has developed a synthetic methodology to prepare an ICL DNA based on the lesion induced by hepsulfam (1,7-heptanediol disulfamate), used clinically in the treatment of chronic myelogenous leukemia (Figure 1a). Colvin and coworkers have shown that hepsulfam can form a number of N^7 alkylated products with deoxyguanosine including 1,7-bis(guanyl)heptane. Studies with synthetic oligonucleotides revealed that hepsulfam forms ICLs at 5'-GXC-3' sites. However, the N^7-alkylated bis adducts (Figure 1b) are unstable limiting their use for structural and biochemical studies to probe DNA repair mechanisms. The synthetic methodology we have developed introduces an alkyl linkage between the two adjacent strands linking the O^6 positions of deoxyguanosine (Figure 1c) to produce the ICL DNA. This cross-link exhibits chemical stability which will enable various structural and biochemical investigations related to DNA repair. Preliminary structural and biophysical characterization of this novel cross-link will be discussed.

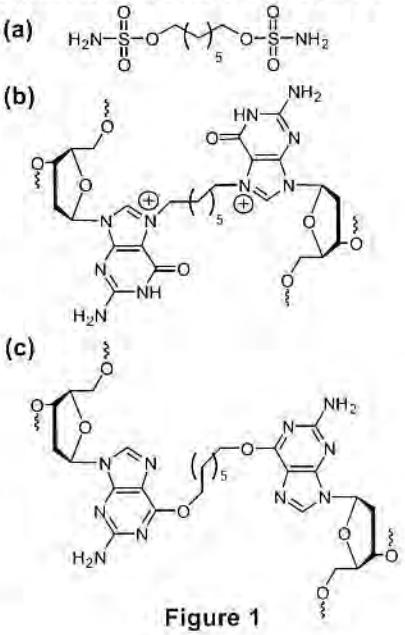


Figure 1

References:

[1] (a) Colvin, M. (1993) Alkylating Agents and Platinum Antitumor Compounds in Cancer Medicine (Lea & Febiger) Philadelphia, p.733-754. (b) Pratt, W.B.; Ruddon, R.W.; Ensminger, W.D.; Maybaum (1994) Covalent DNA-binding drugs in The Anticancer Drugs 2nd Ed. (Oxford Press) New York, p.108-154.

[2] Sancar A., Lindsey-Boltz, LA., Unsal-Kacmaz, K., Linn, S. *Annu Rev Biochem.*, 2004; 73, 39-85.

[3] Dronkert, ML., Kanaar, R. *Mutat. Res.*, 2001; 486, 217-247.

[4] Streeper, RT., Cotter, RJ., Colvin, ME., Hilton, J., Covin, OM. *Cancer Res.*, 1995; 55, 1491-1498.

[5] Wilds, CJ., Booth, JD. and Noronha AM. *Tetrahedron Lett.*, 2006; 47, 9125-9128.

TP125

THE 1, 3 DIPOLAR CYCLOADDITION OF AZOMETHINE YLIDES DERIVED FROM ALPHA AMINO ACIDS WITH ACRYLONITRILE, ACRYLAMIDE AND RELATED COMPOUNDS.

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CSIRO Molecular Health and Technologies

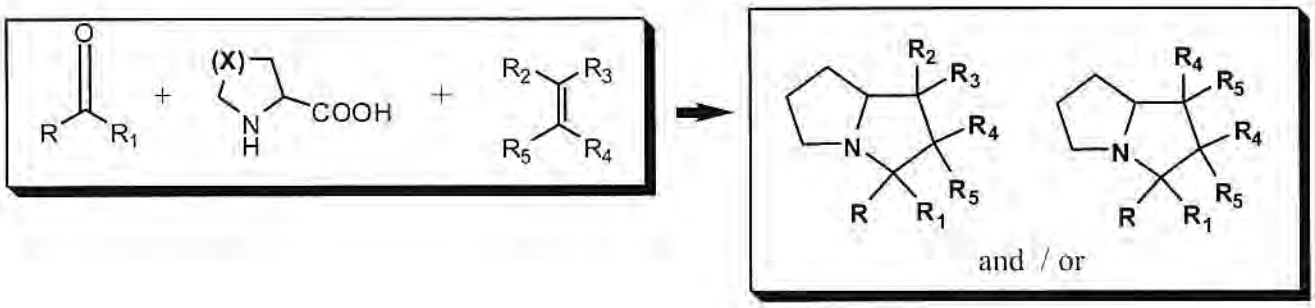
The reaction between an amino acid and a carbonyl compound can lead to the formation of an azomethine ylide, which can further react with an alkene to generate a pyrrolidine via a 1, 3 dipolar cycloaddition reaction.

Substituted, fused and spiro pyrrolidine compounds are a motif found throughout many biological systems. These compounds are utilised in their natural, chemically modified and totally synthetic form by the pharmaceutical industry as drugs and drug candidates. They have been used as anti-depressants, anti bacterial compounds, and some have shown promising anti HIV activity.

In order to explore new areas for possible bioactivity we were interested in diversifying the range of substituents available on the pyrrolidine ring since relatively few variations have been reported.

Accordingly, we decided to synthesise a range of spiro pyrrolidine compounds via the 1, 3 dipolar cycloaddition methodology.

Various carbonyl compounds were reacted with the alpha-amino acids proline, sarcosine, pipecolic acid, and thiaproline to generate the ylide in situ. The ylide thus formed could then be reacted with activated alkenes bearing a nitrile and/or carboxamido group to form the spiro pyrrolidine compound as shown below.



TP126

C(1)-SUBSTITUTED GLYCALS : VERSATILE PRECURSORS TO NOVEL *C*-GLYCOSIDES

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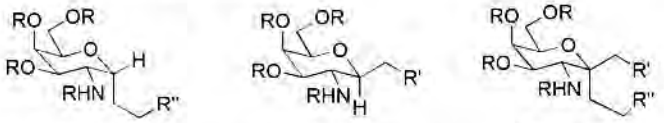
[b] *Novartis Horsham Research Centre, Wimblehurst Road, Horsham, RH12 5AB, UK*

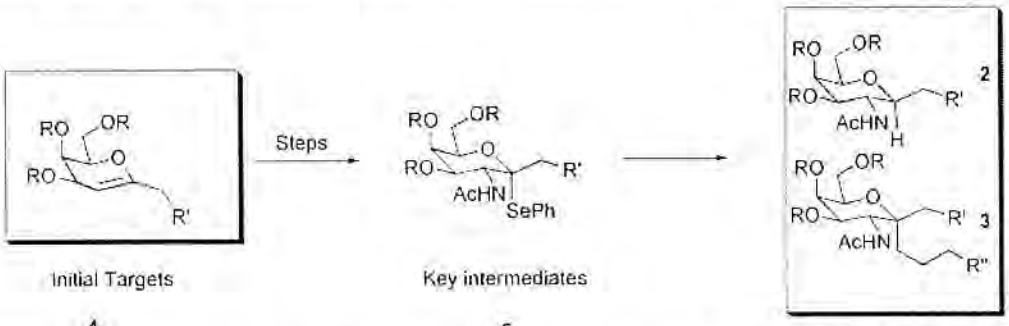
Carbohydrates are fundamentally important in a wide range of biological processes and so there has been a marked increase in the amount of interest into studies concerning the chemistry and biochemistry of these compounds. *C*-Glycosides are heterocyclic molecules where the anomeric oxygen atom of an *O*-glycoside has been replaced with a methylene or another carbon substituent. Despite recent developments in this area, the synthesis of *C*-glycosides still remains a challenging task.



a-*C*-Glycosides 1 | β-*C*-Glycosides 2 | 1,1-Disubstituted *C*-Glycosides 3

Within the Gallagher group work has focused on the conversion of *C*-glycals into *C*-glycosides of 2-amino sugars,[1,2] due to the fact that analogues of 2-amino-sugars have been identified as inhibitors of mucin production. The synthetic route used within the group utilises the very useful azidoselenation reaction.[3] It is anticipated that *C*(1)-substituted glycals (4) could give an entry into β-*C*-glycosides (2) and 1,1-disubstituted *C*-glycosides (3).

The primary aim of this project is to define a general and flexible route to *C*(1)-substituted glycals (4) and use these in the synthesis of the corresponding *C*(1)-selenoglycosides (5) and then the subsequent β-*C*-glycosides (2) or 1,1-disubstituted *C*-glycosides (3).



Initial Targets 4 | Key intermediates 5 | Longer term targets

The route we envisaged to synthesise *C*(1)-substituted glycals (4) would start by converting carbohydrate lactones into the corresponding exocyclic enols, which would then undergo allylic displacement in the presence of palladium or copper catalysts to give rise to a range of *C*(1)-substituted glycals (4) in an efficient and versatile fashion.

References:

(1) SanMartin, R., Tavassoli, B., Walsh, K. E., Walter, D. S., Gallagher, T. *Org. Lett.*, 2000; *2*, 4051-4054.

(2) Grant, L., Liu, Y., Walsh, K. E., Walter, D. S., Gallagher, T. *Org. Lett.*, 2002; *4*, 4623-4625.

(3) Czernecki, S., Randriamandimby, D. *Tetrahedron Lett.*, 1993; *34*, 7915-7916.

TP127

STUDIES TOWARD THE TOTAL SYNTHESIS OF AZINOMYCIN A, A POTENT ANTITUMOR ANTIBIOTIC

Takao Yamaguchi,[1] Yuji Kawada,[1] Kazuyuki Miyashita[1,2] and Takeshi Imanishi[1]

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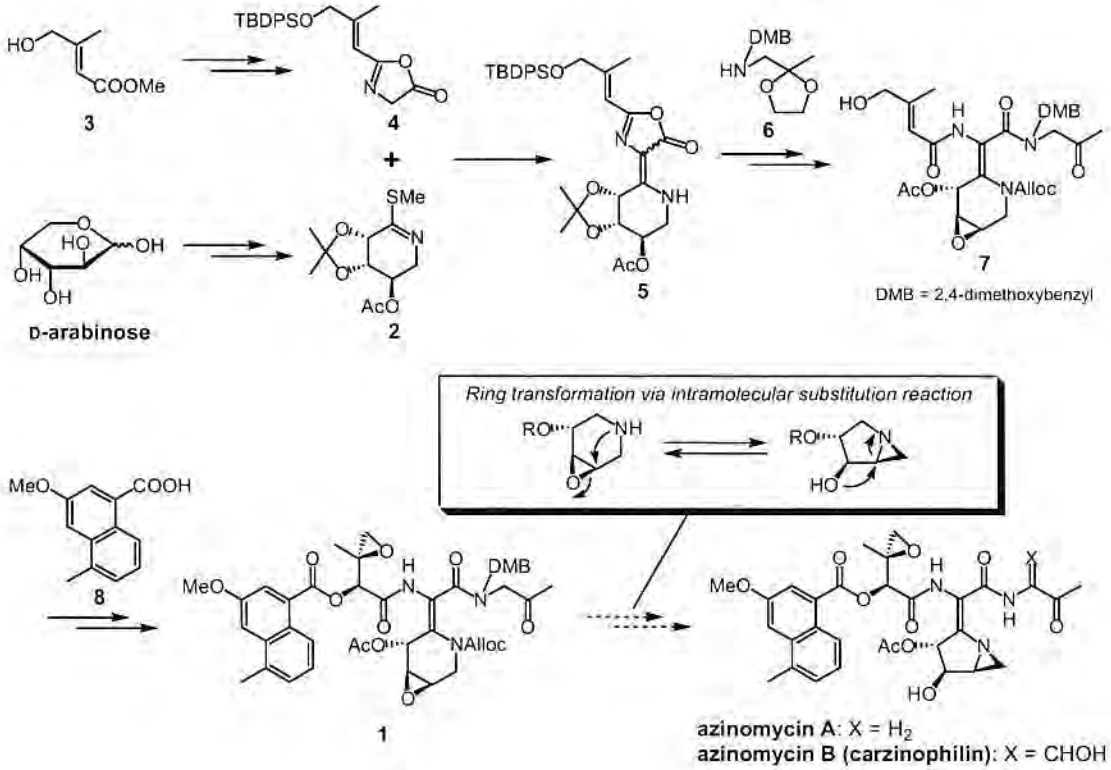
[2]*Faculty of Pharmacy, Osaka Ohtani University*

Azinomycins A and B, isolated from Streptomyces griseofuscus, are an antitumor antibiotic possessing a DNA interstrand cross-linking activity. Synthesis of these natural products is challenging because of the unprecedented, densely functionalized and highly reactive 4-hydroxy-1-azabicyclo[3.1.0]hexane ring system. We previously reported a 3,4-epoxypiperidine structure, a constructional isomer of the 4-hydroxy-1-azabicyclo[3.1.0]hexane ring system, as a novel and simple DNA cleavage molecular unit.[1)] Based on the above result, we believed that interconversion between the two ring systems could be possible, and designed a 3,4-epoxypiperidine derivative 1 as a precursor of azinomycin A. Here we describe the synthesis of 3,4-epoxypiperidine derivative 1.

Thioimidate 2 was prepared from D-arabinose via 11 steps including reductive amination and lactam formation as the key reactions. Treatment of the thioimidate 2 with azlactone 4 which was prepared from unsaturated ester 3 afforded dehydroamino lactone 5. The azlactone ring of 5 was successfully opened by amine 6 to give a dehydropeptide subunit. Then the key 3,4-epoxypiperidine structure of 7 was efficiently constructed via several steps. After asymmetric epoxidation of allyl alcohol moiety of 7, the desired compound 1 was synthesized by condensation with naphthoic acid 8. Conversion of 1 into azinomycin A is in progress, and the details will be presented.



1) Miyashita K., Park M., Adachi S., Seki S., Obika S., Imanishi T. *Bioorg. Med. Chem. Lett.*, 2002; 12, 1075-1077.

TP128

SYNTHETIC STUDIES OF TELOMERASE INHIBITOR UCS1025A

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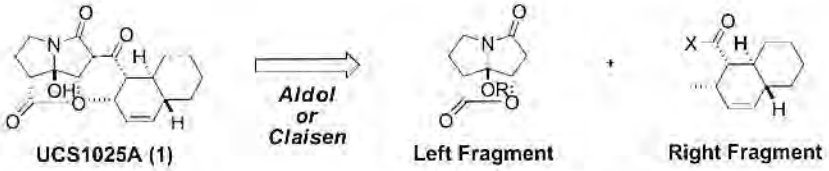
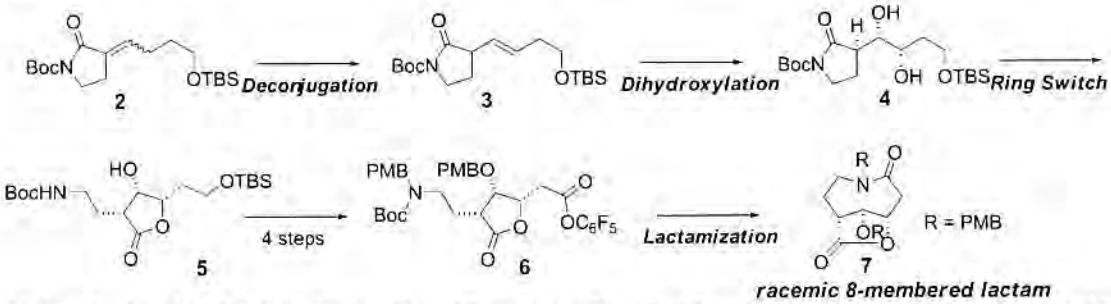
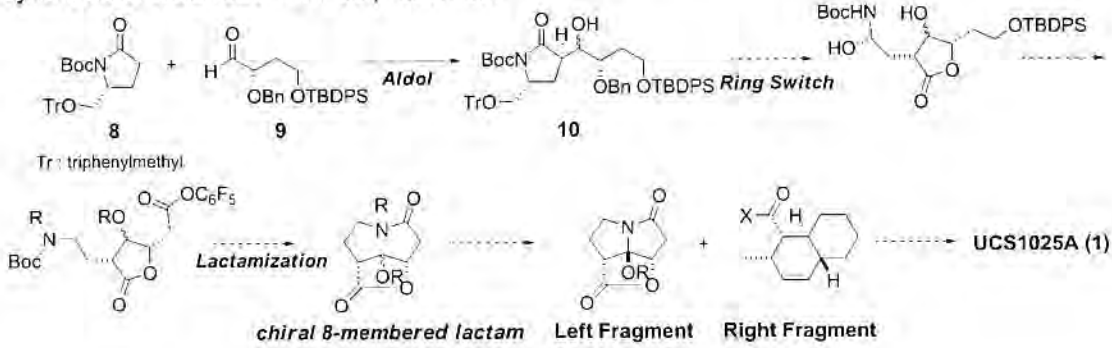
UCS1025A was isolated from the fermentation broth of the *Acremonium* sp. KY4917 fungus. It has been shown to possess antiproliferative properties against human cancer cell lines by inhibiting telomerase.[1] As illustrated in the following scheme, UCS1025A could be synthesized by the coupling of a furopyrrolizidine skeleton (left fragment) and an octahydronaphthalene skeleton (right fragment) *via* an intermolecular aldol or Claisen condensation.



Kinetic deconjugation of the α, β-unsaturated lactam 2 followed by dihydroxylation and acid catalyzed ring switch reaction gave the γ-lactone intermediate 5. Conversion of 5 into the pentafluorophenyl ester 6 and successive lactamization was accomplished to give the 8-membered lactam 7.



Alternatively, chiral aldol intermediate 10 was synthesized from the lactam 8 and the aldehyde 9 to achieve the asymmetric synthesis of the left fragment. Further studies toward the total synthesis of UCS1025A will be presented.



References:
(1) (a) Nakai, R. *J. Antibiot.* 2000; *53*, 294-296. (b) Agatsuma, T. *Org. Lett.* 2002, *4*, 4387-4390.

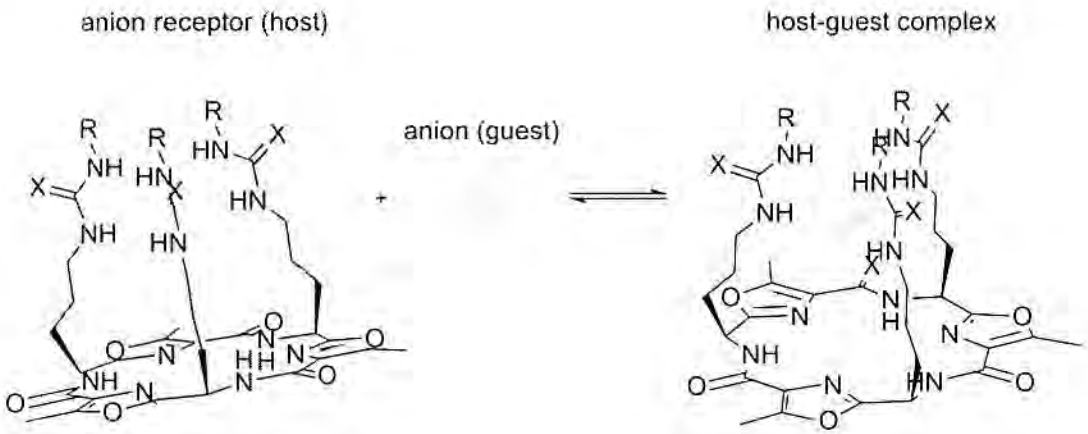
TP129

CYCLIC PEPTIDE MOLECULAR SCAFFOLDS: SYNTHESIS AND ANION BINDING

Philip G. Young, Katrina A. Jolliffe

The University of Sydney, Australia

Azole-modified cyclic peptides are excellent candidates for use as supramolecular structures due to their rigidity, ease of functionalisation and ability to present functional groups in a spatially well-defined manner. Two novel azole-modified cyclic peptides, **1** and **2**, bearing three urea or thiourea groups, respectively, were prepared by the cyclooligomerisation of oxazole structural units. The ability of **1** to bind to bromide anions is evident from ^{1}H NMR titration experiments and provides promising results for the use of such cyclic peptide scaffolds in supramolecular chemistry.



1: X = O, R = 4-nitrophenyl
2: X = S, R = 4-nitrophenyl

References:
[1] Jolliffe, K A, *Supramol. Chem.*, 2005; 17, 81-86.

TP131

N-HETEROCYCLIC AMIDES OF (N-TETRAHYDROISOQUINOLINE)- AND (2-QUINOLYLOXY)ALKANOIC ACIDS AS POTENTIAL PHARMACOLOGICAL AGENTS

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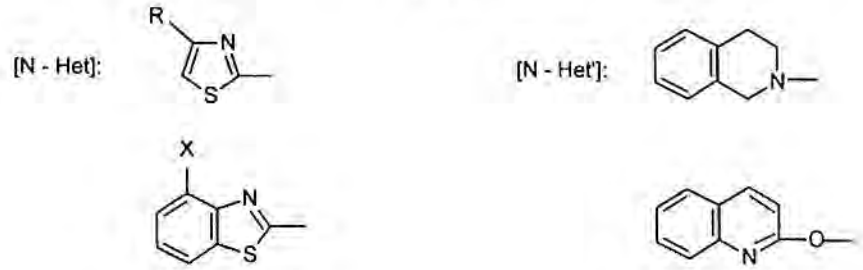
Quinoline derivatives possess antimicrobial, sedative and antitumour properties. Different pharmacological effects of thiazole derivatives, including their anti-inflammatory properties, are also well known. These facts prompted us to synthesize the compounds containing two heterocycles – quinoline or hydrogenated quinoline and thiazole – in one molecule.
For this purpose 1,2,3,4-tetrahydroisoquinoline and 2-chloroacetamido- or 3-chloropropionamido(benzo)thiazoles were reacted to synthesize some 2(3)-(1,2,3,4-tetrahydroisoquinolin-2-yl)-N-(thiazol-2-yl)-, -(benzothiazolyl-2-yl)acet/propionamides with the aim to improve their biological properties. 2(3)-(2-Quinolyloxy)-N-(thiazol-2-yl)- and -(benzothiazolyl-2-yl)acet/propionamides were obtained by reaction of above mentioned amides of chloroalkanoic acids with preliminarily prepared Li salt of 2-hydroxyquinoline.

$$[N - Het] — NHCO(CH_2)_n — [N - Het']$$

$$n = 1, 2$$



R = H, CH_3, p-$CH_3OC_6H_4$; X = H, Cl

The characterization of compounds involved elemental analysis, lipophilicity, ^1H, ^{13}C NMR spectroscopy and X-ray crystallographic analysis.
The compounds were found to be active in psychotropic *in vivo*, anti-inflammatory *in vivo* and cytotoxicity *in vitro* screening.
The cytotoxicity of compounds synthesized was tested *in vitro* on two monolayer tumor cell lines: HT-1080 (human fibrosarcoma), MG-22A (mouse hepatoma), and normal 3T3 cell lines. The compounds are low or non-toxic compounds concerning normal cell lines NIH 3T3 and have selective cytotoxic effects and NO-induction ability on different tumour cell lines.
The action on the CNS was evaluated on indicators of hexenal-induced narcosis, phenamine hyperthermia, phenamine hyperactivity and corazol induced convulsions. The investigated compounds possess marked sedative action.
High anti-inflammatory activity, up to 76% inhibition of mice paw edema, was determined almost for all tested compounds.

TP132

HYDROGENATED QUINOLINE AND ISOQUINOLINE DERIVATIVES AS MONODENTATE LIGANDS FOR NEW BIOLOGICALLY ACTIVE OXORHENIUM BASED COMPLEXES

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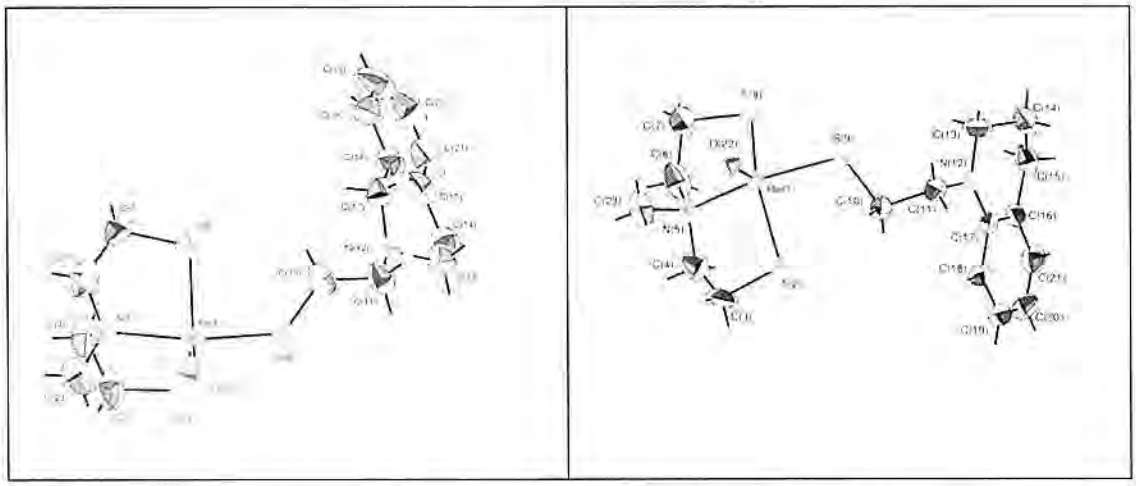
[2]*Forschungszentrum Dresden-Rossendorf, Germany*

The chemical design of metal complexes of the type [Het_NSReO(SNMeS)], where Het_N is hydrogenated quinoline or isoquinoline residue, has been carried out in an approach for better understanding how the nature of their components affect their biological activity. The choice of tetrahydro(iso)quinoline derivatives for pharmacological investigation was stipulated by their potential biological properties. Tetrahydro(iso)quinoline derivatives have been discussed as affine ligands for CNS receptors and possess sedative and antitumour properies. Besides hydrogenated quinoline moieties are present as structural fragments in Amsacrine, Bruneomycinum, Vincristine and Vinblastinum widely used in oncology.
Prompted by the facts mentioned above we have designed some receptor-affine rhenium complexes using tetrahydro(iso)quinolyl moieties as anchor groups. In this paper we report on the synthesis and structural and biological characterization of new oxorhenium adducts where the ligands coordinate to the metal centre in [3+1]-dentate fashion.



N-(Hydroxyethyl)-1,2,3,4-tetrahydroisoquinoline and N-(hydroxyethyl)-1,2,3,4-tetrahydroquinoline have been converted into N-(2-mercaptoxyethyl)-1,2,3,4-tetrahydro(iso)quinolines, monodentate ligands suitable for complexation. N-(2-mercaptoxyethyl)-1,2,3,4-tetrahydroisoquinoline was synthesized from the corresponding aminoalcohol by two different ways: a) its conversion to chloroethyl derivative in reaction with $SOCl_2$ and subsequent treatment with two equivalents of sodium thiophosphate dodecahydrate in dimethylformamide, followed by acid hydrolysis, and also b) by the Mitsunobu procedure: treatment of the alcohols with previously prepared PPh_3-diizopropylazodicarboxylate-thiobenzoic acid system and subsequent hydrolysis. The introduction of a thiol group via thiobenzoate was the method of choice for the tetrahydroquinoline molecule. Complexation was achieved by simultaneous reaction of $[PPh_3]_2[Re(O)Cl_3]$ with preliminarily prepared tridentate HSNMeSH and the corresponding N-heterocycle containing thiol.
The characterization of compounds synthesized involved elemental analysis, IR, ^1H and ^{13}C NMR spectroscopy and X-ray crystallographic analysis.
New compounds were screened for acute toxicity, antitumour and psychotropic properties and were found to be active in this respect.

TP133

SILICA GEL CATALYSED ACETYLATION OF N-(2-METHOXYETHYL)-1,2,3,4-TETRAHYDROISOQUINOLINE WITH ETHYLACETATE

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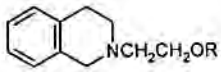
Silica gel can initiate different reactions, this from one side causes difficulties for isolation of compounds by column chromatography, from the other, these reactions can be used as alternative ones, but in some cases as the only possible method, for the synthesis of chemical compounds.
Solid acid catalysts, especially silica gels and zeolites, have received much attention in organic synthesis for their ease in handling and use. The application of solid adsorbents such as alumina and silica gel as solid supports in organic synthesis affords a new procedure for selective reactions involving oxidation, alkylation, condensation, acetylation and monomethyl esterification. The significant potential of adsorbents is due to the milder reaction conditions and simpler work-up required and the selective organic transformations that they allow.
In the course of the separation of N-(2-hydroxyethyl)tetrahydroisoquinoline alkylation products using silica gel column chromatography with ethylacetate as eluent N-(2-acetoxyethyl)-1,2,3,4-tetrahydroisoquinoline has been isolated [1].
Now we report our detailed studies of silica gel catalyzed acetylation of some tetrahydro(iso)quinoline derivatives: N-(2-hydroxyethyl)-1,2,3,4-tetrahydroisoquinoline (**1**) , N-(2-methoxyethyl)-1,2,3,4-tetrahydroisoquinoline (**2**), N-(2-(3'-dimethylheptylsilylpropoxyethyl)-1,2,3,4-tetrahydroisoquinoline (**3**), N-(2-hydroxyethyl)-1,2,3,4-tetrahydroquinoline (**5**), N-(2-methoxyethyl)-1,2,3,4-tetrahydroquinoline (**6**) and N-(2-(3'-dimethylheptylsilylpropoxyethyl)-1,2,3,4-tetrahydroquinoline (**7**).



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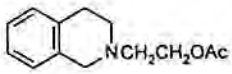

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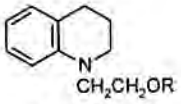

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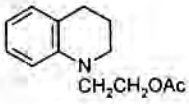

8

1, 5: R = H; **2, 6**: R = Me; **3, 7**:$(CH_2)_3SiMe_2Hp$

The reaction was performed under room temperature with fifty-fold ethylacetate excess and in ratios (silica gel : substrate) of 2.5-25 during 3-72 h. The course of the reaction was followed by GC-MS data.
It was found that acetylation of these compounds by ethylacetate did not take place in the absence of silica gel.
The results of the conversion of N-(2-hydroxyethyl)-1,2,3,4-tetrahydroisoquinoline (**1**) and -1,2,3,4-tetrahydroquinoline (**5**) to N-(2-acetoxyethyl)-1,2,3,4-tetrahydroisoquinoline (**4**) and -1,2,3,4-tetrahydroquinoline (**8**) correspondingly are dependent on silica gel amount and reaction duration.
The chemoselectivity of the silica gel catalyzed acetylation of methoxyethyl and dimethylheptylsilylpropoxyethyl derivatives has been found.

References:
[1] Segal I., Zablotskaya A., Lukevics E., *Chem.Heterocycl. Comp.*, 20

TP134

SYNTHEIS OF NOVEL 5-SUBSTITUTED-6-METHYL-4-[5-CHLORO-3-METHYL-1-PHENYL-1*H*-PYRAZOL-4-YL]-3,4-DIHYDROPYRIMIDIN-2(1H)-ONES

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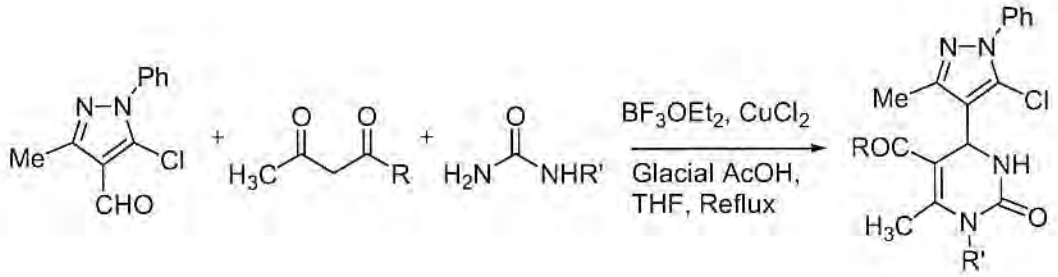
Derivatives of dihydropyrimidones (DHPMS) exhibit a wide range of biological activities and are antihypertensive, antitumor and anti-inflammatory agents. In the past decade, 4-aryldihydropyrimidinones have attracted considerable attention owing to their high activity as calcium channel blockers.

Our aim was to synthesize derivatives of dihydropyrimidines having a heterocyclic ring at the 4 position of the dihydropyrimidine ring. Thus, we combined the 1,4-dihydropyrimidine pharmacophore with the 5-chloropyrazole unit. More recently, several additional reaction conditions for the synthesis of dihydropyrimidinones have been reported. However, in spite of their advantages and potential utility, some of them suffer from drawbacks such as long reaction times, expensive catalysts or lower yields. We now report an efficient synthesis of new dihydropyrimidin-2(1*H*)-ones having a 5-chloropyrazole unit at position 4 of the dihydropyrimidine ring.



TP135

SYNTHESIS OF HIGH-FUNCTIONAL 2',5'-OLIGOADENYLATES AND THEIR BIOLOGICAL ACTIVITIES

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RNase L is activated by binding of unusual 2',5'-kinked oligoadenylates (2-5A) and acts as the effecter enzyme of the 2-5A system, an interferon-induced anti-virus mechanism. Efforts have been made to understand the 2-5A binding mechanism, not only for scientific interests but also for the prospects that the understanding of such mechanism lead to new remedies for viral diseases. We have recently elucidated the crystal structure of the 2-5A binding ankyrin repeat domain of human RNase L complexed with 2-5A. On binding 2-5A at the ankyrin-repeat domain, RNase L forms a homodimer and removes the ankyrin-repeat domain from the nuclease domain to become the active form. The observation may indicate that first and third adenosine residues are important for the activation of RNase L. The second adenosine residue is not necessary for the activation.

In this paper, we describe synthesis of 2',5'-oligoadenylate (2-5A) analogs having the methylene moieties at the second adenosine residue of 2-5A and their biological activities.

TP136

APPLICATION OF MICROWAVES IN PALLADIUM-CATALYZED SYNTHESIS OF PYRIDOINDOLES

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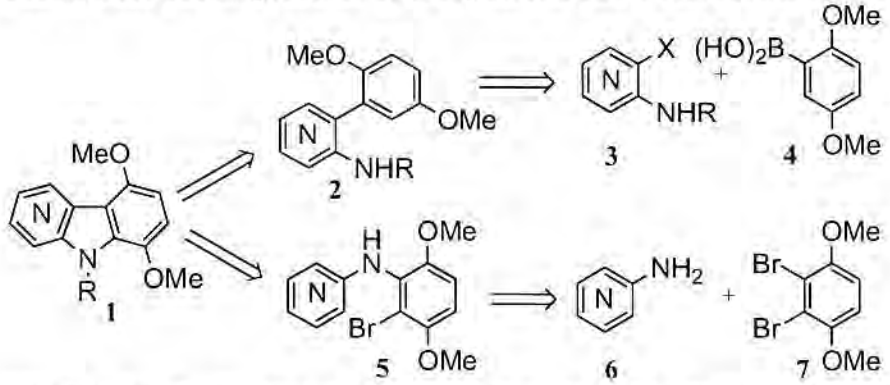
Within the search of new heterocyclic compounds with antitumor like properties, an attractive target are molecules that have a carbazol basic skeleton fused with another heterocyclic system such as ellipticine, ellipticine quinones and calothrixin.[1]
Considering that the preparation of aza-analogues of these compounds has received little attention, the synthesis of aza-ellipticine quinones was undertaken. In this context we were interested in the application of palladium-catalyzed reactions to obtain pyridoindol **1**.

Suzuki cross-coupling reaction of phenylboronic acid **4** with several haloaminopyridine



derivatives under microwaves irradiation gave the corresponding pyridoaryl compounds **2** in 47-63%. Furthermore, palladium-catalyzed amination of aryldibromide **7** with aminopyridines **6** under microwaves irradiation afforded 33-56% of anilinopyridines **5**. Progress towards the synthesis of pyridoindol **1** using palladium-catalyzed reactions will be described.

Acknowledgements: This study was supported by FONDECYT, Research Grant 1060592.

1. D. Mal, B. K. Senapati, P. Pahari, Tetrahewdron, **2007**, *63*, 3768, and references therein.

Wednesday 18th July Keynote & Plenary Speaker Abstracts

TOTAL SYNTHESIS OF COMPLEX HETEROCYCLIC NATURAL PRODUCTS

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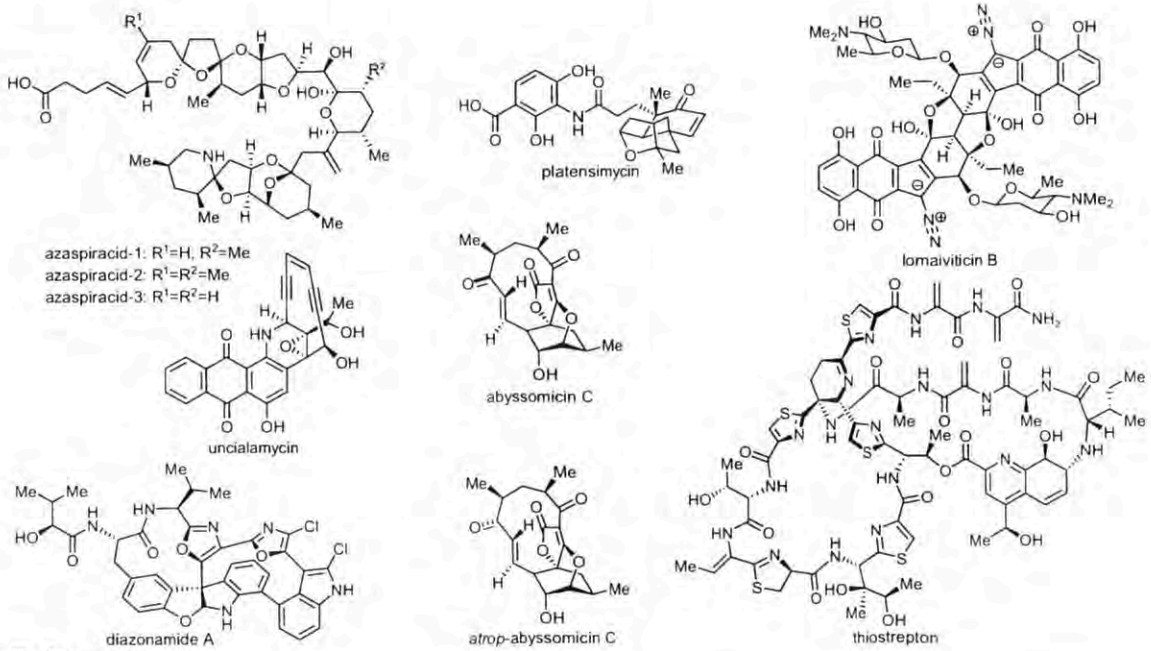
Natural Products have historically provided synthetic chemists with fertile platforms for discovery and development in the area of chemical synthesis, chemical biology and medicinal chemistry. Such opportunities continue to fascinate and deliver new science as new structures come under scrutiny by synthetic chemists. In this lecture, a number of total synthesis endeavors, targeting complex heterocyclic molecules such as the ones shown below, will be discussed with emphasis on inventions in chemistry, biology and medicine.



References:

Nicolaou, K.C. *J. Org. Chem.*, 2005, *70*, 7007-7027.
Nicolaou, K.C. *J. Med. Chem.*, 2005, 48, 5613-5638.
Nicolaou, K.C., Bulger, P.G., Sarlah, D. *Angew. Chem. Int. Ed.*, 2005, 44, 4490-4527.
Nicolaou, K.C., Bulger, P.G., Edmonds, D. *Angew. Chem. Int. Ed.*, 2006, 45, 7134-7186.

SYNTHESIS OF MODIFIED NUCLEOSIDES FOR METAL DEPOSITION IN AND AROUND DNA

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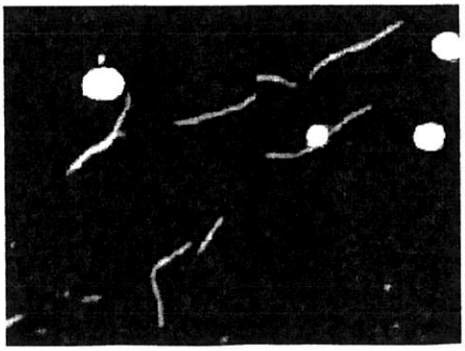
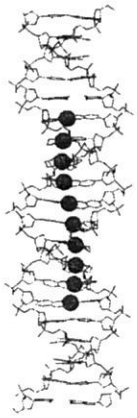
The Carell laboratory prepares highly modified nucleosides for biochemical[1] and nanomaterials[2] application. In this lecture I will focus at our results obtained in the DNA materials research field[2a-c]. DNA is currently intensively exploited to create nanostructures. In order to functionalize DNA based nanostructures we explore the concept to combine chemical synthesis, "click-chemistry" and molecular biology methods to attach metal ions and metallic metals (M^0) to DNA in order to create conductive nanowires. The first approach is based on the concept of metal ion base pairs. Here the canonical base pairs are replaced by synthetic metal ion coordinating units. DNA assembly induces formation of an array of complexing ligands, which capture metal ions and deposite them on top of each other inside the DNA duplex. In the second approach we use DNA purely as a template to finally deposite metallic silver and gold around the DNA duplex. To this end we synthesize modified nucleobases, which can be incorporated into DNA using either solid phase chemistry or PCR. In this way one obtains modified DNA strands containing up to 2000 bp. The introduced modifications allow the selective deposition of metals around the DNA structure using the Tollens reaction and subsequent Ag-development. This procedure allows to create DNA based conductive nanowires.





References

1. a) F. Brueckner, U. Hennecke, T. Carell, P. Cramer, *Science* **2007**, *315*, 859-862; b) W. J. Schreier, T. E. Schrader, F. O. Koller, P. Gilch, C. E. Crespo-Hernández, V. N. Swaminathan, T. Carell, W. Zinth, B. Kohler, *Science* **2007**, *315*, 625-629; c) A. Mees, T. Klar, P. Gnau, U. Hennecke, A. P. M. Eker, T. Carell and L.-O. Essen, *Science* **2004**, *306*, 1789-1793; d) G. W. Hsu, M. Ober, T. Carell, L. S. Beese, *Nature* **2004**, *431*, 217-221.

2. a) G. A. Burley, J. Gierlich, M. R. Mofid, H. Nir, S. Tal, Y. Eichen, T. Carell, *J. Am. Chem. Soc.* **2006**, *128(5)*, 1398-1399 and *Science* **2007**, *311*, 437; b) G. H. Clever, K. Polborn, T. Carell, *Angew. Chem. Int. Ed.* **2005**, *44(44)*, 7204-7208; c) K. Tanaka, G. H. Clever, Y. Takezawa, C. Kaul, M. Shionoya and T. Carell, *Nature Nanotech.* **2006**, *1*, 190-194 and *Nature* **2006**, *444*, 698.

NEW CATALYSIS CONCEPTS

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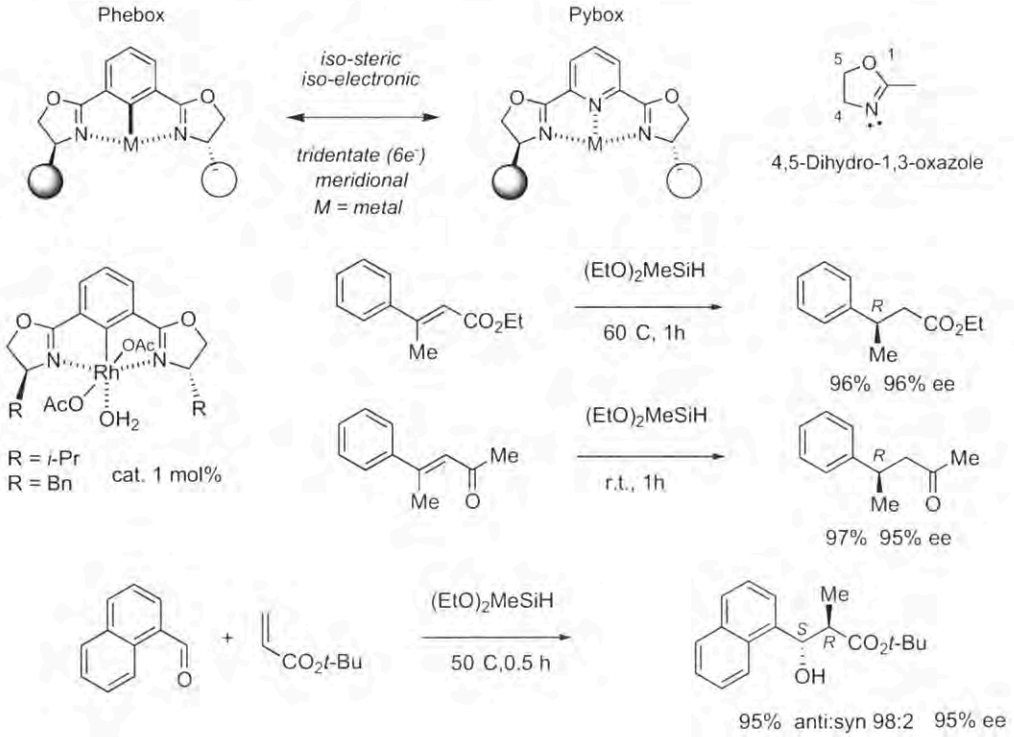
"Organocatalysis: the field." Over the last ten years, the field of organocatalysis has grown from a small collection of chemically unique or unusual reactions to a thriving area of general concepts, atypical reactivities and broadly useful reactions. While the modern era of organocatalysis still remains in its infancy, growth in this new chemical field continues to move at a breathtaking pace.
In this presentation, we will demonstrate a variety of new and valuable transformations based on the paradigms of iminium-activation, enamine-activation, acid catalysis and SOMO catalysis. We will also highlight an alternative strategy for natural product synthesis that we hope will provide the strategic foundations to bypass the "taxol problem."

CHIRAL PHENYL-BIS(OXAZOLINE) AS AN EFFICIENT AUXILIARY FOR ASYMMETRIC CATALYSIS

Hisao Nishiyama

Graduate School of Engineering, Department of Applied Chemistry, Nagoya University

Synthesis of organic auxiliaries for transition-metal complexes is a very important subject in the field of molecular catalysis and organic synthesis including asymmetric synthesis, because the auxiliaries can provide appropriate stereochemical and electronic environments around active metal centers controlling catalysis. We have developed the heterocyclic oxazoline skeleton, 4,5-dihydro-1,3-oxazole, as a modular unit of multidentate auxiliaries, because the oxazoline can supply sufficient substituent diversity at 4- and 5-chiral centers by use of a variety of β-aminoalcohols. We first reported pyridine-bis(oxazoline) [pybox] as a tridentate oxazoline-based ligand for asymmetric catalysis. Despite it's tridentate nature, dissociation of pybox from metals was observed, and extra addition of ligand was necessary for catalysis. This fact promoted us to come up with new tridentate auxiliary, phenyl-bis(oxazoline) [phebox], which adopts C_2-symmetric and meridional configuration with a central covalent bond to transition-metals. Here, we will describe synthesis of phebox auxiliaries, their transition-metal complexes, and asymmetric catalyses, which are asymmetric hydrosilylation of alkenes, conjugate reduction of α,β-unsaturated carbonyl compounds, and asymmetric reductive aldol coupling of acrylates and carbonyl compounds. We will also show remote electronic effect for asymmetric catalysis and organometallic reactions on the phebox-metal skeletons.



References:

1) Desimoni G., Faita G., Quadreil P., *Chem. Rev.*, 2003; 103, 3119-3154.
2) Nishiyama H., *Chem. Soc. Rev.*, 2007; in press.
3) Kanazawa Y., Tsuchiya Y., Kobayashi K., Shiomi T., Ito J., Kikuchi M., Yamamoto Y., Nishiyama H., *Chem. Eur. J.*, 2006; *12*, 63-71. Kanazawa Y., Nishiyama H., *Synlett*, 2007; 3343-3345.
4) Nishiyama H., Shiomi T., *J. Am. Chem. Soc.*, 2005; *127*, 6972-6973.
5) Ito J., Shiomi T., Nishiyama H., *Adv. Synth. Catal.*, 2006; *348*, 1235-1240. Shiomi T., Ito J., Yamamoto Y., Nishiyama H., *Chem. Eur. J.*, 2006; 5594-5600.
6) Ito J., Miyakawa T., Nishiyama H., *Organometallics* 2006; *25*, 5216-5218.

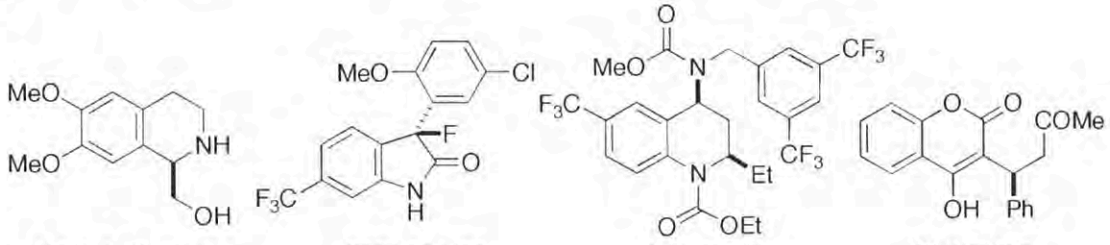
Thursday 19th July Keynote & Plenary Speaker Abstracts

ENANTIOSELECTIVE SYNTHESIS OF HETEROCYCLIC COMPOUNDS BASED ON PALLADIUM ENOLATE CHEMISTRY

Mikiko Sodeoka

Synthetic Organic Chemistry Lab, RIKEN

We have found that the chiral Pd aqua and μ-hydroxo complexes work as a mild Brønsted acid and base catalyst. The chiral Pd enolates were generated by the proton abstraction and reacted with various electrophiles under acidic conditions. Highly enantioselective Michael addition,[1-3] Mannich-type reaction,[4-6] aldol reaction, and fluorination,[7-10] have been achieved. Pd-catalyzed addition of amines and hydride to α,β-unsaturated carbonyl compounds also proceeded enantioselectively to generate Pd enolates.[11,12]
These reactions are useful for the synthesis of various optically active heterocyclic compounds. Examples of the heterocyclic compounds synthesized using these reactions are shown below.



(*R*)-calicotomine BMS-204352 torcetrapib (S)-warfarin

References:

[1] Hamashima, Y.; Hotta, D.; Sodeoka, M. *J. Am. Chem. Soc.* 2002, *124*, 11240-11241.
[2] Hamashima, Y.; Hotta, D.; Umebayashi, N.; Tsuchiya, Y.; Suzuki, T.; Sodeoka, M. *Adv. Synth. Cat.* 2005, *347*, 1576-1586.
[3] Hamashima, Y.; Suzuki, T.; Takano, H.; Shimura, Y.; Tsuchiya, Y.; Moriya, K.; Goto, T.; Sodeoka, M. *Tetrahedron*, 2006, *62*, 7168-7179.
[4] Hamashima, Y.; Sasamoto, N.; Hotta, D.; Somei, H.; Umebayashi, N.; Sodeoka, M. *Angew. Chem. Int. Ed.* 2005, *44*, 1525-1529.
[5] Sasamoto, N.; Dubs, C.; Hamashima, Y.; Sodeoka, M. *J. Am. Chem. Soc.* 2006, *128*, 14010-14011.
[6] Hamashima, Y.; Yagi, Takano, H.; Tamás, L.; Sodeoka. M. *J. Am. Chem. Soc.* 2002, *124*, 14530-14531.
[7] Hamashima, Y.; Takano, H.; Hotta, D.; Sodeoka. M. *Org. Lett.* 2003, *5*, 3225-3228.
[8] Hamashima, Y.; Suzuki, T.; Takano, H.; Shimura, Y.; Sodeoka, M. *J. Am. Chem. Soc.* 2005, *127*, 10164-10165.
[9] Suzuki, T.; Goto, T.; Hamashima, Y.; Sodeoka, M. *J. Org. Chem.* 2007, *72*, 246-260.
[10] Hamashima, Y.; Sodeoka, M. *Synlett* 2006, 1467- 1478.
[11] Hamashima, Y.; Somei, H.; Shimura, Y.; Tamura, T.; Sodeoka, M. *Org. Lett.* 2004, *6*, 1861-1864.
[12] Tsuchiya, Y.; Hamashima, Y.; Sodeoka, M. *Org. Lett.* 2006, *8*, 4851-4854.

HETEROCYCLIC CLEFT SHAPED RECEPTORS FOR MOLECULAR RECOGNITION AND TRANSPORT

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Our interests in molecular recognition have led us to synthesise a variety of different families of receptor[1] for anions (e.g. **1**)[2], ion-pairs (e.g. **2**)[3] and neutral guests (e.g. **3**),[4] many of which contain heterocyclic components (Figs 1-3)[1] Our latest results in this area will be discussed in this lecture.

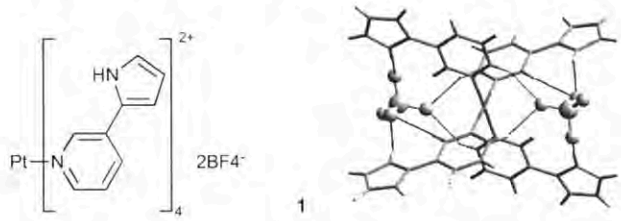

Fig 1 A platinum templated metal-organic anion receptor **1**. Crystal structure is shown (right).

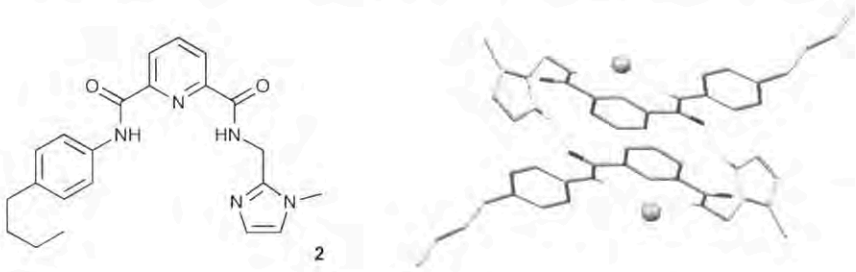

Fig 2 A H^+/Cl^- co-transporter **2** based on a pyridine-2,6-dicarboxamide backbone that functions in POPC and POPC/cholesterol lipid bilayers (left) and the crystal structure of the HCl complex of the receptor (right) showing dimer formation in the solid state.

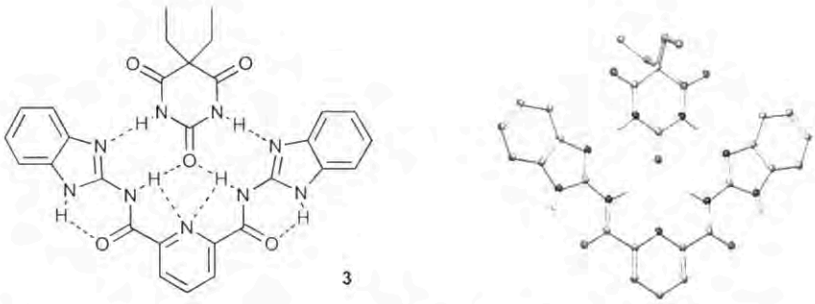

Fig 3 A pyridine-2,6-dicarboxamide functionalised with two benzimidazole substituents (left) forms complexes with barbtal and a variety of ureas in solution and the solid-state stabilised *via* intramolecular hydrogen bonding interactions in the receptor. The X-ray crystal structure of a barbital complex is shown (right).

References:
1 Gale, PA. *Acc. Chem. Res.* 2006; 39, 465-475; Gale PA. *Chem. Commun.* 2005; 3761-3772.
2 Vega IED, Gale PA, Light ME, Loeb SJ. *Chem. Commun.* 2005; 4913-4915.
3 Gale, PA, Garric J, Light ME, McNally B, Smith BD. submitted for publication.
4 Fisher MG, Gale PA, Light ME. manuscript in preparation.

TOTAL SYNTHESIS OF HETEROCYCLIC NATURAL PRODUCTS

Thorsten Bach

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For some time, our group has been working on the synthesis of heterocyclic natural products. By using photochemical methods, the syntheses of (±)-oxetin[1] and of (+)-preussin[2] were achieved using the Paternò-Büchi reaction as the key step. More recently, enantioselective photochemical methods[3] have been developed, which are currently applied to the synthesis of alkaloids and terpenoid natural products. The heterocyclic polyketide antibiotic (+)-wailupemycin B was synthesized from the chiral pool starting material (+)-carvone.[4]

Multiply substituted aromatic heterocycles have been synthesized using regioselective cross-coupling and metalation reactions. Various eupomatenoids were prepared to illustrate the key features of regioselective cross-coupling chemistry on benzofurans.[5] Naturally occurring thiazoles, which were synthesized in our group, include the antifungal dithiazole (+)-cystothiazole E[6] and the endothelin converting enzyme inhibitor WS75624 A.[7] Current work has been concerned with the total synthesis of the thiazolylpeptide antibiotic GE2270 A.[8]

The lecture will provide a summary on the status of our work in the area of heterocyclic natural product synthesis highlighting both the underlying methods and their application to more complex structures.

References:

[1] Bach T, Schröder J. *Liebigs Ann./Recueil*, 1997, 2265-2267.
[2] Bach T, Brummerhop H. *Angew. Chem. Int. Ed.*, 1998, 37, 3400-3402. Bach T, Brummerhop H, Harms K. *Chem. Eur. J.*, 2000, 6, 3838-3848.
[3] Bach T, Bergmann H, Grosch B, Harms K. *J. Am. Chem. Soc.*, 2002, 124, 7982-7990. Bauer A, Westkämper F, Grimme S, Bach T. *Nature*, 2005, 436, 1139-1140.
[4] Kirsch S, Bach T. *Angew. Chem. Int. Ed.*, 2003, 42, 4685-4687. Kirsch SF, Bach T. *Chem. Eur. J.*, 2005, 11, 7007-7023.
[5] Bach T, Bartels M. *Synthesis*, 2003, 925-939.
[6] Bach T, Heuser S. *Angew. Chem. Int. Ed.*, 2001, 40, 3184-3185. Bach T, Heuser S. *Chem. Eur. J.*, 2002, 8, 5585-5592.
[7] Bach T, Heuser S. *Synlett*, 2002, 2089-2091.
[8] Heckmann G, Bach T. *Angew. Chem. Int. Ed.*, 2005, 44, 1199-1201. Delgado O, Heckmann G, Müller HM, Bach T. *J. Org. Chem.*, 2006, 71, 4599-4608.

GUANINE OXIDATION LEADING TO HYDANTOINS: FROM ORGANIC SYNTHESIS TO BIOLOGY

Cynthia J. Burrows

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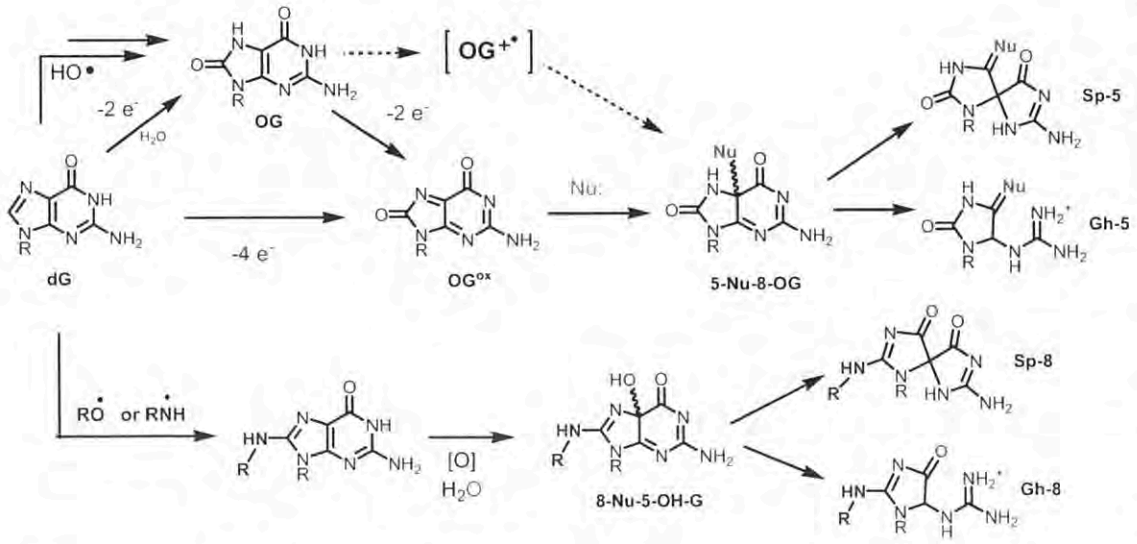
The heterocyclic bases in genomic and mitochondrial DNA are subject to oxidative damage leading to G-to-T and G-to-C transversions and frameshift mutagenesis. Our laboratory studies the organic chemistry of guanine oxidation and uses the incorporation of synthetically modified guanine lesions into oligonucleotides to study the biological responses of DNA processing enzymes to this damage. Cellular oxidation of guanosine most commonly leads to 8-oxoguanosine (OG), but alternative pathways and further oxidation of OG yield the hydantoin products spiroiminodi-hydantoin (Sp) and guanidinohydantoin (Gh).[1] Mechanistic studies suggest the intermediacy of a quinonoid intermediate (OG^{ox}),[2] that is trapped by a nucleophile such a solvent water molecule (Nu: = HO or O). The intermediate OG^{ox} can also form covalent adducts with amines under oxidizing conditions. Amines studied include spermine,[3] an abundant polyamine at mM concentrations in the nucleus, and the lysine side chains of proteins; the latter leads to DNA-protein cross-link formation.[4] Detailed characterization of the products of oxidized guanine-lysine adduct indicates that both Gh and Sp-like structures are formed, and that the position of adduction, C5 vs. C8 of G, depends on the mechanism of oxidation of G. Singlet oxygen reactions that proceed via OG^{ox} lead to C5 adducts while one-electron (or Type I photochemical) reactions lead to adduction at C8. This suggests that isolation of specific DNA lesions could provide a signature of the cell's exposure to oxidative stress.



References:

1. Luo W, Muller JG, Rachlin EM, Burrows CJ. *Org. Lett.* 2000; 2, 613-617.
2. Ye Y, Muller JG, Luo W, Mayne CL, Shallop AJ, Jones RA, Burrows CJ, *J. Am. Chem. Soc.* 2003; 126, 9540-9541
3. Hosford ME, Muller JG, Burrows CJ *J. Am. Chem. Soc.* 2004; 126, 9540-9541
4. Johansen ME, Xu X, Muller JG, Burrows CJ. *Biochemistry* 2005;

Thursday 19th July
Mathews Theatre A
Invited Lectured & Contributed Oral Presentations
1:30pm-3:00pm

ENANTIOSELECTIVE SYNTHESIS OF VITAMIN E AND HETEROCYCLES USING DOMINO PD-CATALYZED TRANSFORMATIONS

Lutz F. Tietze

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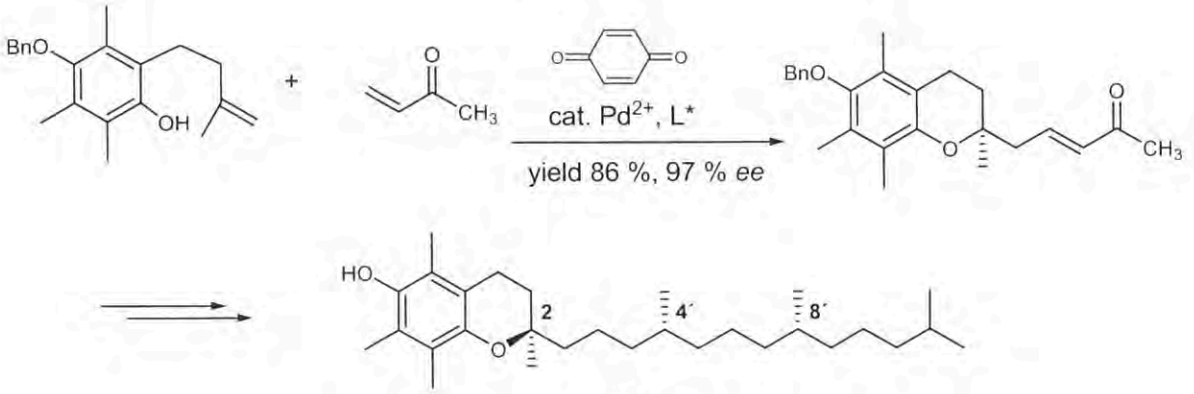
Synthesis of relevant organic compounds such as natural products and analogues, drugs, diagnostics, agrochemicals and any kind of material is a main topic in academic and industrial chemistry. An important goal in this field is the improvement of synthetic efficiency, moreover, other essential issues are the care for our environment, the preservation of our resources and economical advantages.

A general way to improve synthetic efficiency and also address the other criteria is the development of catalytic domino and similar processes.[1]



Vitamin E

In the lecture the use of domino Pd-catalyzed transformations for the efficient enantioselective synthesis of vitamin E [2] and heterocycles [3] will be described.

References:

[1] L.F. Tietze, G. Brasche, K. Gericke, *Domino Reactions in Organic Synthesis*, Wiley VCH, Weinheim 2006. [2] a) L. F. Tietze, K. M. Sommer, J. Zinngrebe, F. Stecker, *Angew. Chem. Int. Ed.* 2005, *44*, 257-259. b) L.F. Tietze F. Stecker, J. Zinngrebe, K.M. Sommer, *Chem. Eur. J.* 2006, *12*, 8770-8776 [3] L.F. Tietze, K.F. Wilckens, S. Yilmaz, F. Stecker, J. Zinngrebe, *Heterocycles* 2006, *70*, 309-319.

STEREOCONTROLLED SYNTHESES OF FUNCTIONALISED TETRAHYDROPYRANS

Christine L. Willis

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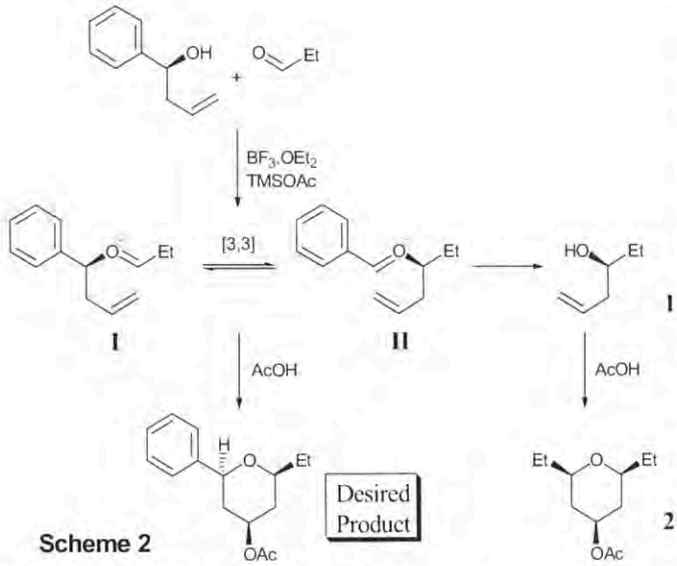
Substituted tetrahydropyrans are common structural features of a diverse range of natural products and biologically important molecules. The Prins cyclisation is a valuable method for the stereoselective construction of these oxygen heterocycles which enables the creation of up to 3 new stereogenic centres in a single-pot process with excellent stereocontrol (Scheme 1).[1]

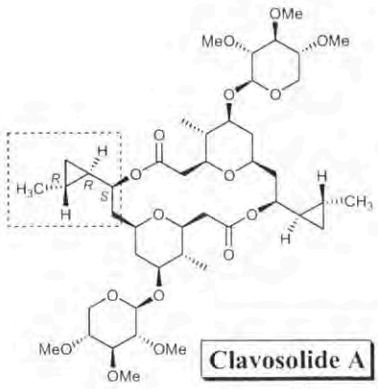
Scheme 1



Scheme 2

The mechanism of the Prins cyclisation is not simple and under certain conditions may be accompanied by an oxonia-Cope rearrangement and allyl exchange processes (Scheme 2).[2] This leads to the formation of unwanted byproducts such as homoallylic alcohol 1 and symmetrical tetrahydropyran 2. For example, the relative stability of the charged intermediates I and II plays a key role in determining the outcome of the reaction, with electron donating groups stabilising a neighbouring oxonium ion *via* resonance. Therefore, prudent choice of disconnection is essential in designing routes to synthetic targets.

Armed with knowledge of the mechanism, the Prins cyclisation has been applied to the total synthesis of several natural products for example the macrodiolide clavosolide A,[3] which was isolated from a marine sponge,[4] and two catechols.



Important contributions to this work have been made by: Roger Alder, Conor Barry, Jon Elsworth, Gregory Parker, Peter Seden- University of Bristol Nick Bushby and John Harding - AstraZeneca. We are grateful to the EPSRC, AZ and the University of Bristol for funding.

References:

1. Barry, CS, Crosby, SR, Harding, JR, Hughes, RA., King, CD, Parker, GD, Willis, CL. *Org. Lett.*, 2003; *5*, 2429-2432.
2. (a) Jasti, R, Rychnovsky, SD, *J. Am. Chem. Soc.*, 2006; 128, 13640-13648; (b) Barry, CS, Bushby, N, Harding, JR, Hughes, RA, Parker, GD, Roe, R, Willis, CL *Chem. Comm.*, 2005; 3727-3729.
3. Barry, CS, Elsworth, JD, Seden, PT, Bushby, N, Harding, JR, Alder, RW, Willis, CL. *Org. Lett.*, 2006; *8*, 3319-3322.
4. (a) Rao, MR, Faulkner, DJ. *J. Nat. Prod.*, 2002; *65*, 386-388; (b) Erickson, KL, Gustafson, KR, Pannell, LK, Beutler, JA, Boyd, MR *J. Nat. Prod.*, 2002; *65*, 1303-1306.

PRACTICAL, ONE-POT, THREE-COMPONENT SYNTHESIS OF N-HETEROCYCLIC CARBENE (NHC)-LIGATED PALLADACYCLES AND THEIR USE AS WELL-DEFINED PRECATALYSTS FOR Pd-MEDIATED CROSS-COUPLING REACTIONS.

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In the recent years, bulky, *N*-aryl-substituted N-heterocyclic carbenes (NHC) have emerged as high-performance ligands in Pd-mediated cross-coupling reactions.[1] However, complexation of NHCs to Pd is not trivial. While catalytically active, catalytic brews prepared in situ from NHC precursors (e.g., imidazolium salts) and common sources of Pd, do not allow control of the catalyst yield and chemical composition, resulting in waste of precious metal and poor reproducibility.[2] Therefore, the use of well-defined, monoligated complexes of bulky NHCs with Pd has become the dominant strategy to overcome this drawback.[3] Palladacycles ligated with NHCs[4] are excellent candidates for development of air stable, highly active cross-coupling catalysts. When submitted into the reaction conditions, the palladacycle moiety is degraded with rate dependence on the temperature and the nature of the cyclometallated ligand and the co-reactants. The active catalyst, a monoligated NHC-Pd species is thus released in a controlled manner. However, the current synthetic methods for the preparation of NHC-palladacycle adducts require the use of highly moisture- and air-sensitive isolated carbenes and purified palladacycles, which are often prepared in low yields under harsh conditions. Therefore, the development of a more practical method employing easily accessible materials will be necessary if the potential of NHC-palladacycles in catalysis is to be fully realized. Recently, we have developed a novel protocol for NHC-palladacycle synthesis relying on a one-pot, three-component, sequential reaction between imidazolium salts, $PdCl_2$ and *N*-benzyldimethylamine. The preparation of NHC-palladacycle adducts by this methodology will be presented, as well the use of these complexes as well-defined precatalysts in Pd-mediated transformations of highly substituted aromatic and heterocyclic substrates.

References:

(1) Kantchev, EAB; O'Brien, CJ; Organ, MG *Aldrichimica Acta* 2006; 39, 97-111.

(2) (a) Hadei, N; Kantchev, EAB.; O'Brien, CJ; Organ, MG *J. Org. Chem.* 2005; 70, 8503-8507. (b) Lebel, H; Janes, MK; Charette, AB; Nolan, SP *J. Am. Chem. Soc.* 2004; 126, 5046-5047.

(3) (a) O'Brien, CJ; Kantchev, EAB; Valente, C; Hadei, N; Chass, GA; Lough, A; Hopkinson, A C; Organ, MG *Chem. Eur. J.* 2006; 12, 4743-4748. (b) Marion, N; Navarro, O; Mei, J; Stevens, ED; Scott, NM; Nolan, SP *J. Am. Chem. Soc.* 2006; 128, 4101-4111. (c) Marion, N; Ecarnot, EC; Navarro, O; Amoroso, D; Bell, A; Nolan, SP *J. Org. Chem.* 2006; 71, 3816-3821. (d) Singh, R; Viciu, MS; Kramareva, N; Navarro, O; Nolan, SP *Org. Lett.* 2005; 7, 1829-1832. (e) Selvakumar, K; Zapf, A; Spannenberg, A; Beller, M *Chem. Eur. J.* 2002; 8, 3901-3906.

(4) (a) Navarro, O; Marion, N; Oonishi, Y; Kelly III, R. A; Nolan, SP *J. Org. Chem.* 2006; 71, 685-692 (b) Frey, GD; Schütz, J; Herdtweck, E; Herrmann, WA *Organometallics* 2005; 24, 4416-4426.

PHOSPHORUS HETEROCYCLIC CHEMISTRY: NEW STRUCTURES AND REACTIONS

Streubel*, R., Özbolat, A., Helten, H., and Perez, J. M.

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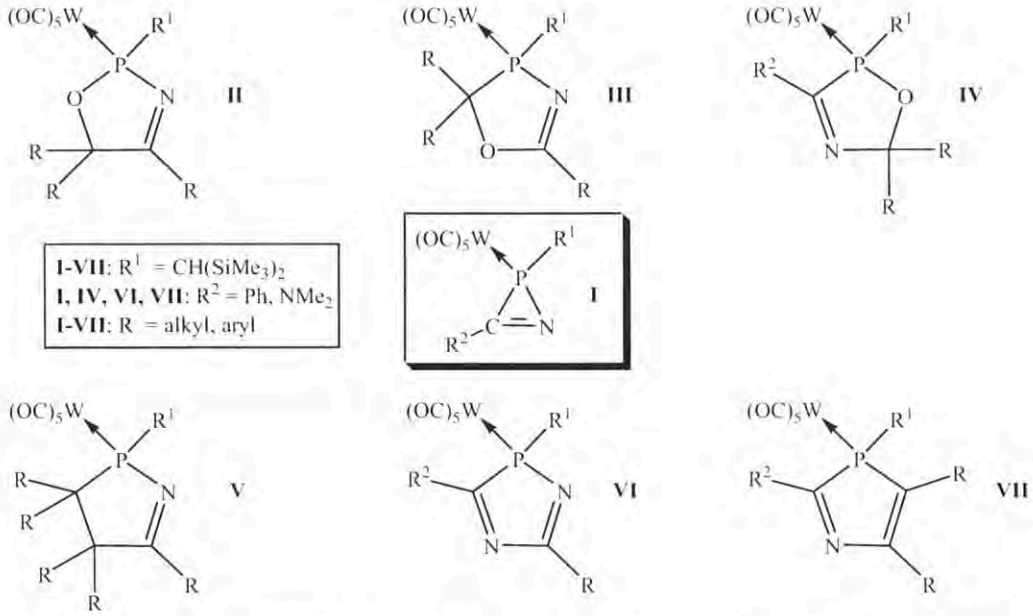
Gaining mild access to small- and medium-sized heterocycles and to use them as starting materials for new and selective transformations are current synthetic challenges in phosphorus chemistry. 2*H*-Azaphosphirene complexes might serve as a good case-in-point, e.g., we have shown that they are well suited for thermal, photochemical and even catalytical reactions.[1] Here we report on the use of 2*H*-azaphosphirene complexes I in the synthesis of 1,3,2-oxazaphosphole-3-ene II,[2] 1,3,4-oxazaphosphol-2-ene II,[3] 1,3,5-oxazaphosphole-4-ene IV,[4] 1,2*H*-azaphosphole-5-ene V,[5] 2*H*-1,4,2-diazaphosphole complexes VI[6] and 3*H*-1,3-azaphosphole complexes VII[7] (Scheme). A new access to I will be reported, too.[8]



NMR data, X-ray structures and DFT studies on various reaction courses using model systems will be presented and discussed.

References:

[1] Review: Streubel, R.; *Coord. Chem. Rev.* 2002, 227, 175. [2] a) Rohde, U.; Ruthe, F.; Jones, PG.; Streubel, R.; *Angew. Chem. Int. Ed.* 1999, *38*, 215; b) Streubel, R.; Jones, PG.; Streubel, R.; unpublished. [3] a) Wilkens, H.; Ruthe, F.; Jones, PG:; Streubel, R.; *Chem. Eur. J.* 1998, *4*, 1542; b) Hoffmann, N.; Streubel, R.; Ricard, R.; Tran Huy, NH.; Mathey, F.; *C. R. Chimie* 2004, *7*, 927. [4] a) Neumann, C.; Prehn Junquera, A.; Wismach, C.; Jones, PG.; Streubel, R.; *Tetrahedron* 2003, *59*, 6213b) Streubel, R.; Perez, JM. Nieger, M.; unpublished. [5] a) Hoffmann, N.; Jones, PG.; Streubel, R.; *Angew. Chem. Int. Ed.* 2002, *41*, 1226; b) Streubel, R.; Wilkens, H.; Ruthe, F.; Jones, PG.; *Organometallics* 2006, *25*, 4830. [6] Helten, H.; Nieger, M.; Schnakenburg, G.; Streubel, R.; submitted. [7] Helten, H.; Streubel, R.; unpublished. [8] Özbolat, A.; von Frantzius, G.; Nieger, M.; Streubel, R.;

Thursday 19th July
Mathews Theatre B
Invited Lectured & Contributed Oral Presentations
1:30pm-3:00pm

SYNTHETIC INVESTIGATION OF HAPLOPHYTINE – ARCHITECTURALLY COMPLEX HETERO-DIMERIC INDOLE ALKALOID

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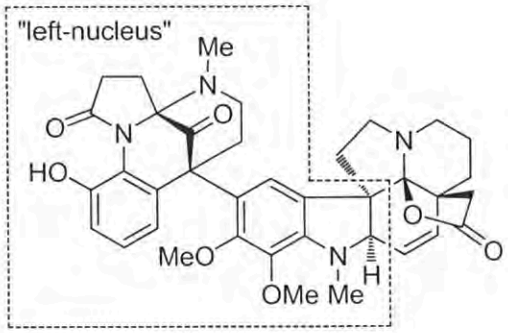
Synthesis of the "left" structural domain of haplophytine (**1**) is reported. The strategy features a stereoselective oxidative construction of its sterically congested carbon–carbon bond (C9'–C15) and an efficient cascade sequence involving a skeletal rearrangement of a presumed epoxide intermediate.



1: haplophytine

References:

1) P. Yates, F. N. MacLachlan, I. D. Rae, M. Rosenberger, A. G. Szabo, C. R. Willis, M. P. Cava, M. Behforouz, M. V. Lakshmikantham, W. Zeiger, *J. Am. Chem. Soc.* **1973**, *95*, 7842–7850.
2) P. D. Rege, Y. Tian, E. J. Corey, *Org. Lett.* **2006**, *8*, 3117–3120.
3) K. C. Nicolaou, U. Majumder, S. P. Roche, D . Y.-K. Chen, *Angew. Chem. Int. Ed.*, **2007**, accepted.

PROSPECTING FOR PHEROMONES: HETEROCYCLES FROM ELEPHANTS AND MANED WOLVES

Thomas E. Goodwin[1], Margaret Weddell[1], Joi Chen[1], Stephen Jackson[1], Bruce Schulte[2] L.E.L. Rasmussen[3†], Nucharin Songsasen[4], William K. Baker[5] and Johannes P.F.G. Helsper[6]

[1]Hendrix College, Department of Chemistry, Conway, AR 72032 USA; [2]Georgia Southern University, Department of Biology, Statesboro, GA 30460 USA; [3]OGI School of Science & Engineering (OHSU), Department of Environmental & Biomolecular Systems, Beaverton, OR 97006 USA ([†] Deceased); [4] Department of Reproductive Sciences, Conservation & Research Center, Smithsonian's National Zoological Park, Front Royal, VA 22630 USA; [5]Little Rock Zoo, 1 Jonesboro Drive, Little Rock, AR 72205 USA; [6]Plant Research International, Wageningen, The Netherlands.

Compared to the large number of chemical signals identified in insects, only a small number of proven mammalian pheromones are known (Burger, B.V. In: Schulz, S. (Ed.), *Topics Curr. Chem.* 2005; *240*, 231-278). Two of these have been identified in elephants: (1) (*Z*)-7-dodecen-1-yl acetate, a sex pheromone in many species of moths, is a urinary signal to males of impending ovulation in female Asian elephants (*Elephas maximus*) (Rasmussen, L.E.L. et al. *Nature* 1996; *379*, 684); (2) frontalin, a well-known beetle aggregation pheromone, is a multifaceted chemical signal in temporal gland secretions of male Asian elephants in musth (Greenwood, D.R. et al. *Nature* 2005; *438*, 1097-1098). We have used solid phase microextraction (SPME; Arthur, C.L. and Pawliszyn, J. *Anal. Chem.* 1990; *62*, 2145-2148) coupled with gas chromatography-mass spectrometry (GC-MS) to search for analogous semiochemicals in African elephant (*Loxodonta africana*) secretions and excretions. We have identified, *inter alia*, unique farnesol derivatives (Goodwin, T.E. et al. *J. Nat. Prod.* 2002, *65*; 1319-1322) and heterocyclic bisnorsesquiterpenes (Goodwin, T.E. et al. In: Mason, R.T. et al. (Eds.) *Chemical Signals in Vertebrates 10* 2005; Springer, NY, pp. 128-139). More recently we have employed the powerful and relatively new technique of automated solid phase dynamic extraction (SPDE; Lipinski, J. *Fresenius' J. Anal. Chem.* 2001; *379*, 57-62) and GC-MS to discover the heterocyclic beetle aggregation pheromones *endo*- and *exo*-brevicomin and frontalin (and their acyclic beetle biochemical precursors) in the headspace over female African elephant urine, thus suggesting their possible role in chemical signaling (Goodwin, T.E. et al. *J. Chem. Ecol.* 2006; *32*, 1849-1853). In addition to our elephant research, we have recently begun to examine possible urinary chemical signaling by another endangered species, maned wolves (*Chrysocyon brachyurus*), which are native primarily to Brazil. Maned wolves, often described as a "fox on stilts", are estimated to number only a few thousand animals in the wild. There is currently an ongoing effort to maintain viable ex situ populations as a possible hedge against extinction, as well as to provide a research resource from which the biology and chemistry of these animals can be better understood. Maned wolf excreta are highly malodorous, and are believed to function in chemical communication via scent marking. Sulfur-containing compounds, possibly arising from high cysteine concentrations, have been proposed as the primary odorants. We have analyzed the headspace over male and female maned wolf urine using automated SPDE/GC-MS. Our studies have revealed not only the presence of a large number of pyrazines, many of which are known insect pheromones (Brophy, J.J. In: Atta-ur-Rahman (Ed.) *Studies in Natural Product Chemistry* v. 5, 1989; Elsevier, NY, pp. 221-275), but also for the first time sulfur-containing compounds (including a thiophene derivative) which are likely contributors to the distinctive maned wolf odors.

PALLADIUM-CATALYZED CROSS-COUPLING REACTIONS IN THE FIELD OF CHROMONOIDS AND FLAVONOIDS

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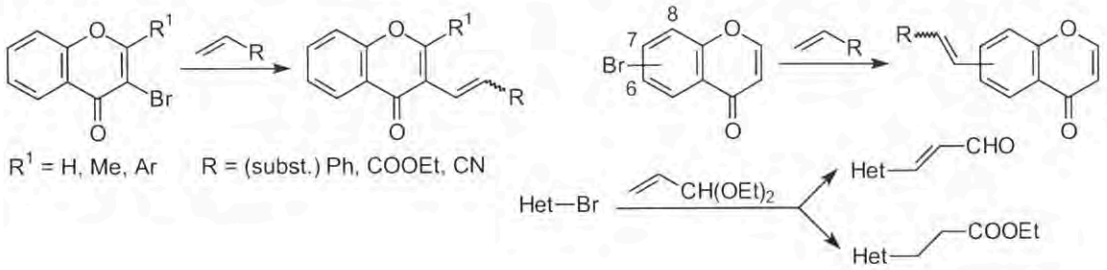
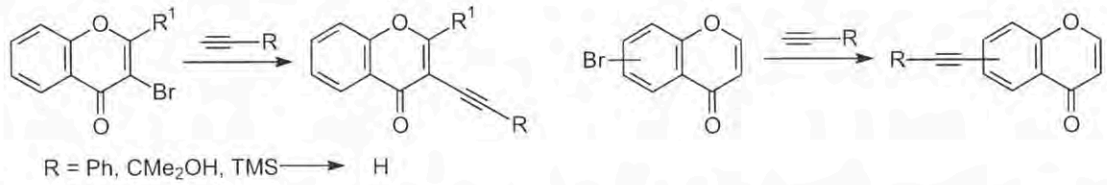
Although metal-catalyzed cross-coupling reactions became a widely used tool for the C-C bond formation among the nitrogen-containing heterocycles, their utilization in the field of oxygen heterocycles is much more sporadic. In our contribution we wish to present our selected results on the use of the Heck and Sonogashira reactions for synthesis of various new chromones and flavones.

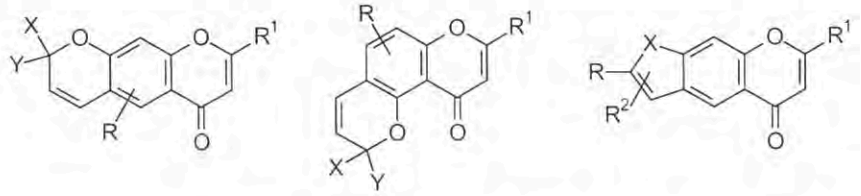
3-Bromochromone and 6-, 7- or 8-bromochromones were alkenylated with the various terminal alkenes under either traditional and or "phosphine-free" conditions with moderate-to-excellent yields depending on the conditionos and substrates used. A marked difference was observed in the reactivity of the 6- and 7- or 8-bromochromones what could be explained in terms of steric factors or stabilization/destabilization exerted by the substituents on the organopalladium intermediate. When acrolein diacetal was used as alkene component both 3-chromonylpropenal (product of the regular β elimination) and ethyl 3-chromonylpropanoate (product of the concurrent β' elimination) was obtained.



Sonogashira reaction of the same substrates resulted in the formation of the expected 1-chromonyl-2-(un)substituted acetylenes in good yields.



Our results demonstrate the usefulness of the cross-coupling reactions among chromonoid systems. This methodology was successfully extended to the chromones carrying an adjacent phenolic group which opens up the way to a new synthetic approach of naturally occurring polycyclic derivatives. Preliminary results on this chemistry will also be presented.



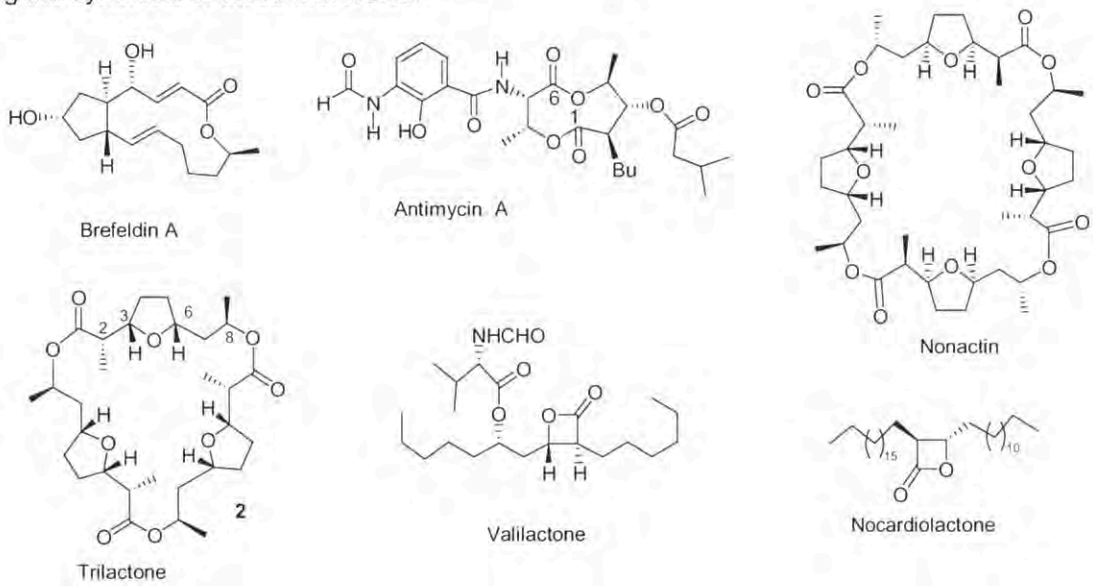
Acknowledgement: Financial support was provided by Hungarian Scientific Research Fund (OTKA NI 61336) and Péter Pázmány Programme (NKTH, RET 006/2004).

ENANTIOSELECTIVE SYNTHESIS OF SOME NATURAL LACTONES

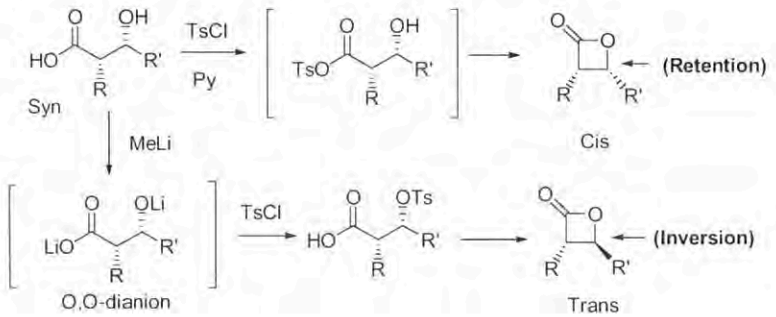
Yikang Wu

State Key Laboratory of Bioorganic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences. e-mail: yikangwu@mail.sioc.ac.cn

Enantioselective total synthesis of several naturally-occurring lactones, including brefeldin A,[1] antimycin A_{3b},[2] nocardiolactone,[3] valilactone,[4] nonactin[5] and trilactone (the proposed structure in the literature), is presented. All these molecules contain hidden aldol partial structures. Those in the first two targets were directly derivable from syn aldol (readily accessible from Evans asymmetric aldolization). In the latter four cases, however, configuration inversion at the position β to a carbonyl group was required if using syn aldols as the precursors. Two types of β inversions were developed during the synthesis of these molecules.



In many cases, the β-lactone ring could also be built directly[6] from syn α,β-disubstituted β-hydroxy acids by selective hydroxyl group activation via corresponding *O,O*-dianions generated by treatment of the acids with excess amounts of MeLi. Under such conditions, the stereochemical outcome is different from that of the classical Adams[7] lactonization.



References:
(1) Wu YK. Shen X. Yang YQ. Hu Q. Huang JH. *J. Org. Chem.* 2004; 69, 3857-3865.
(2) Wu YK. Yang YQ. *J. Org. Chem.*, 2006; 71, 4296-4301.
(3) Sun YP. Wu YK. *Synlett*, 2005; 1477-1479 & *Synlett*, 2006; 1132 (Erratum).
(4) Wu YK. Sun, YP. *J. Org. Chem.* 2006; 71, 5748-5751.
(5) Wu YK. Sun YP. *Org. Lett.*, 2006; 8, 2831-2834.
(6) Wu YK. Sun YP. *Chem. Comm.*, 2005; 1906-1908.
(7) Adams W. Baeza J. Liu JC. *J. Am. Chem. Soc.* 1972; 94, 2000-2006.

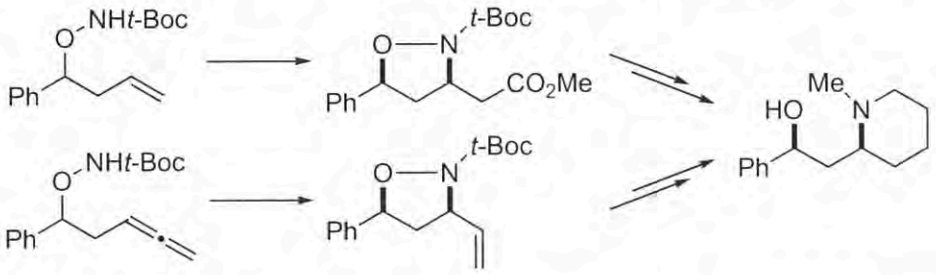
Thursday 19th July
Mathews Theatre C
Invited Lectured & Contributed Oral Presentations
1:30pm-3:00pm

N,O-HETEROCYCLES AS SYNTHETIC INTERMEDIATES

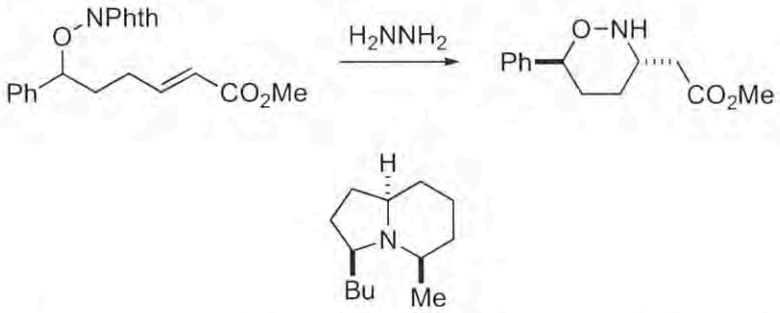
Roderick W. Bates, Lu Yongna and Song Ping and Cai Peiling Melody

Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, 1 Nanyang Walk, Block 5, Level 3, Singapore 637616

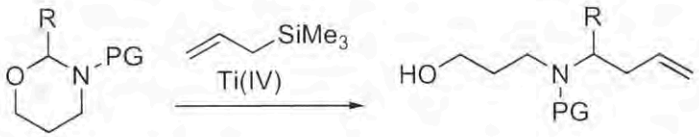
The synthesis and use of two types of *N,O*-heteroycles will be described. We have previously shown that hydroxylamines with either alkene[1] or allene[2] containing substituents can undergo stereoselective metal-catalysed cyclisation. The products have been converted to the alkaloid, sedamine.[2,3]



We have now shown that *N,O*-heterocycles can be synthesized by intramolecular hetero-Michael addition. This chemistry has been applied to the synthesis of an indolizidine alkaloid, monomorine, utilising a tandem hydrogenation-cyclisation procedure.



The members of our second class of *N,O*-heterocycles are cyclic *N,O*-acetals. We have shown that these compounds undergo efficient ring opening under Lewis acid catalysis. Regiochemical and stereochemical issues of this reaction will be discussed.



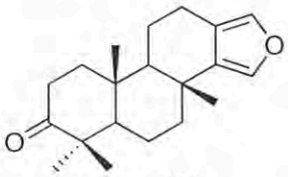
References:
1. Bates R.W., Sa-Ei K., *Org. Lett.*, 2002, *4*, 4225.
2. Bates R.W., Nemeth J., Snell R., *manuscript in preparation*
3. Bates R.W., Boonsombat J., *Org. Biomol. Chem.*, 2005, *3*, 520.

NOVEL FURANOTERPENE METABOLITES FROM MARINE ORGANISMS

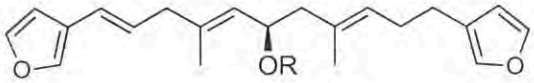
Ken W L Yong, Michael J. Somerville and Mary J Garson

School of Molecular and Microbial Sciences, The University of Queensland, Brisbane 4072, Queensland, Australia

Contemporary marine natural products research addresses the bioactive metabolites that are produced by marine organisms, then how these are produced, and finally why they are produced. Consequently research in this field not only "bioprospects" for new and exciting compounds with biomedical or agrochemical potential, but also explores biosynthesis, symbiosis and chemical ecology



(**1**)



(**2a**) R = $CO(CH_2)_{11}CHMe_2$
(**2b**) R = $CO(CH_2)_{10}CHMeCH_2Me$
(**2c**) R = $CO(CH_2)_{13}Me$

In this presentation, I will give a selection of some of our recent chemical studies with marine invertebrates (sponges and mollusks) that have provided furanoterpene metabolites.[1,2]

References:
[1] Somerville MJ, Mollo E, Cimino G, Rungprom W, and Garson MJ J. Nat. Prod. 2006, 69, 1086-1088.
[2] Somerville MJ, Hooper JNA, and Garson MJ J. Nat. Prod., 2006, 69, 1587-1590.

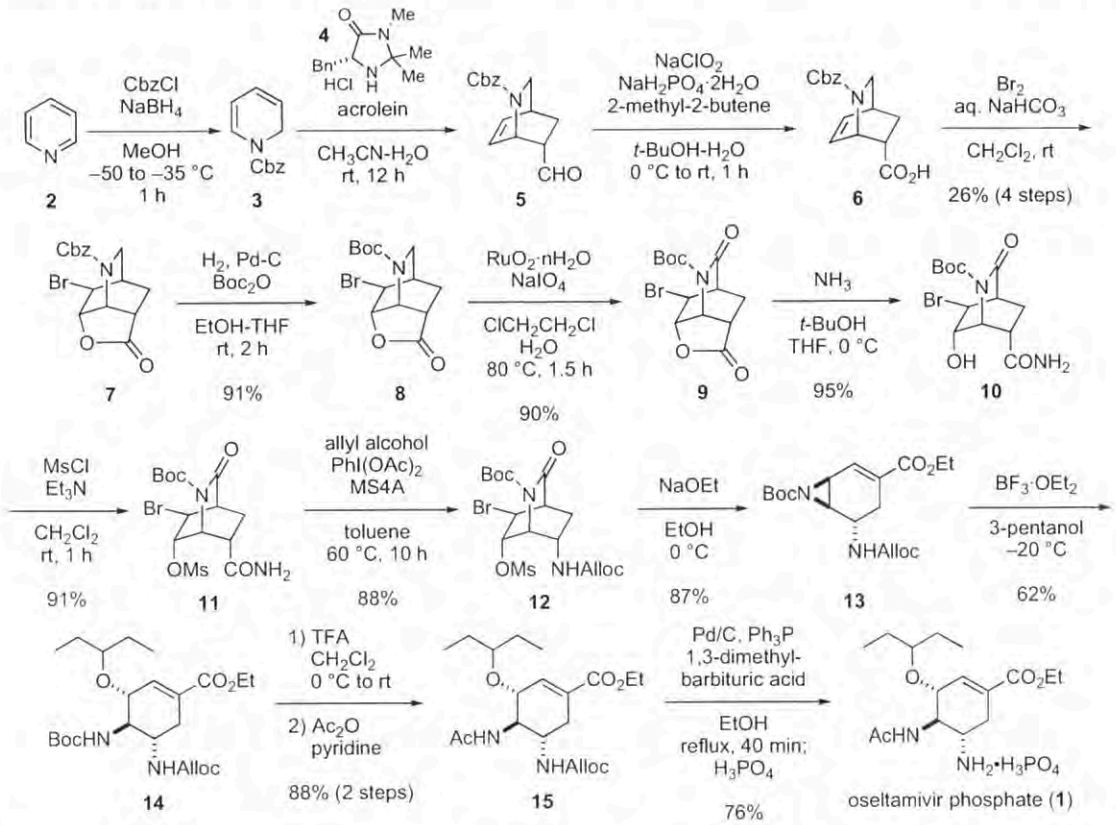
A PRACTICAL SYNTHESIS OF OSELTAMIVIR

Satoshi Yokoshima, Nobuhiro Satoh, Takahiro Akiba, and Tohru Fukuyama

Graduate School of Pharmaceutical Sciences, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan, and Process Chemistry Labs., Astellas Pharma Inc., 160-2, Akahama, Takahagi-shi, Ibaraki 318-0001, Japan

(–)-Oseltamivir phosphate (1, tamiflu®) is a potent inhibitor of neuraminidase and is used worldwide as a drug for type A as well as type B influenza.[1] The recent spread of the avian virus H5N1 has promoted governments to stockpile tamiflu as a precautionary measure against pandemic flu. However, the price of tamiflu is still too expensive for developing countries to stockpile the drug due mainly to the multi-step synthetic route. Namely, the industrial synthesis of oseltamivir employs shikimic acid as a starting material, which is obtained by extraction of Chinese star anise or by fermentation using *E. coli*. In addition, special equipment is needed to handle the explosive intermediates and reagents. Therefore, novel synthetic routes of oseltamivir have been intensively explored.[2]

We have developed a practical synthesis of oseltamivir from pyridine, featuring an asymmetric Diels-Alder reaction of dihydropyridine using MacMillan catalyst,[3] a bromolactonization, Hofmann rearrangement with $PhI(OAc)_2$, and domino transformation of a bicyclo[2.2.2] system into an aziridine intermediate. The key intermediate 7 was obtained as crystals without tedious purifications and could be transformed into 1 in 22% yield. In light of the use of inexpensive reagents and simple operations involved, we are convinced that our synthesis is a viable alternative to the one currently employed for commercial production of tamiflu.



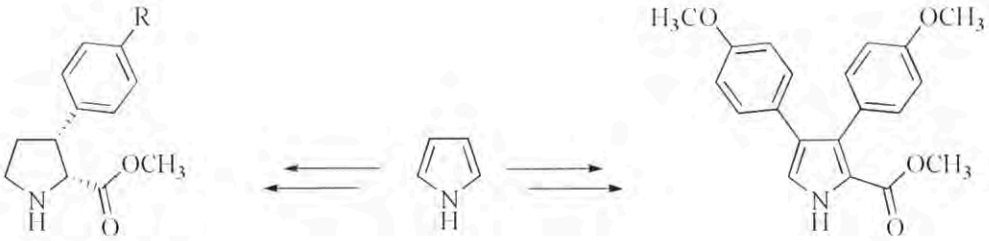
References: (1) Kim, C. U.; Lew, W.; Williams, M. A.; Liu, H.; Zhang, L.; Swaminathan, S.; Bischofberger, N.; Chen, M. S.; Mendel, D. B.; Tai, C. Y.; Laver, W. G.; Stevens, R. C. *J. Am. Chem. Soc.* 1997, *119*, 681. (2) (a) Yeung, Y.-Y.; Hong, S.; Corey, E. J. *J. Am. Chem. Soc.* 2006, *128*, 6310. (b) Fukuta, Y.; Mita, T.; Fukuda, N.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* 2006, *128*, 6312. (c) Mita, T.; Fukuda, N.; Roca, F. X.; Kanai, M.; Shibasaki, M. *Org. Lett.* 2007, *9*, 259. (d) Yamatsugu, K.; Kamijo, S.; Suto, Y.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* 2007, *48*, 1403. (3) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* 2000, *122*, 4243.

REGIO AND CHEMOSELECTIVE REACTIONS OF PYRROLE: TOWARDS SELECTIVELY SUBSTITUTED PYRROLES AND PROLINE ANALOGUES

Ng, Sarah, Smith Jason A.

School of Chemistry, University of Tasmania, Hobart Tasmania, Australia

Pyrrole is a unique aromatic molecule as it can readily undergo substitution at all five positions however, obtaining the desired regioisomer can prove difficult to control. If the regioselectivity of the substitution reactions could be controlled, then pyrrole would be useful as a template for the synthesis of substituted pyrrolidines. We now report the controlled substitution of the pyrrole nucleus and the elaboration of these products into selectively substituted proline and pyrrolidine analogues. The key to regioselective introduction of substituents is the selective halogenation of the ring. Chloride acts as a blocking group at the most nucleophillic site while iodide can be introduced at the less active sites. Selective substitution of the iodide through the Suzuki–Miyaura reaction followed by removal of the chloride allows the preparation of C3- and C5-aryl derivatives.[1] The pyrrole nucleus can then be reduced to yield the corresponding proline derivatives. We have extended this methodology to the synthesis of the 3,4-diaryl derivative lamellarin O dimethyl ether, an intermediate in the synthesis of lukinol A.[2] We are currently exploring the reduction of these systems to selectively form *cis* or *trans* aryl proline derivatives, such as the constrained phenylalanine derivative formed from 3-aryl pyrroles, and pyrrolidines of biological interest.



R = H, OH

References:
1. Smith JA, Ng S and White J. *Organic & Biomolecular Chemistry*, 2006; 4, 2477-2482.
2. Bullington J, Wolff R. and Jackson PJ. *Org. Chem.*, 2002; 67, 9439-9442.

Thursday 19th July
Mathews Theatre D
Invited Lectured & Contributed Oral Presentations
1:30pm-3:00pm

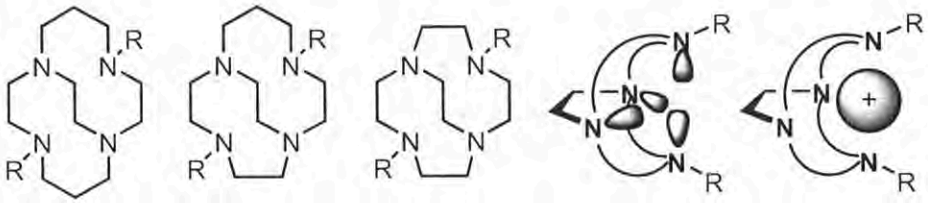
CROSS-BRIDGED TETRAAMINE LIGANDS – SYNTHESIS AND RADIOPHARMACEUTICAL APPLICATIONS

Gary R. Weisman,[1] Edward H. Wong,[1] Yijie Peng,[1] Shanta Bist,[1] Jeffrey S. Condon,[1] Hua Zhou,[1] Antoinette Y. Odendaal,[1] Dannon J. Stigers,[1] David. J. Martin,[1] Matthew J. Young,[1] David J. Tranchemontagne, Jonathan Bryde,[1] Peter C. B. Widger,[1] and Carolyn J. Anderson[2]

[1] *Department of Chemistry, University of New Hampshire, Durham, New Hampshire 03824 U.S.A*

[2] *Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, Missouri 63110 U.S.A.*

Cross-bridged tetraamines have proven to be versatile and useful ligands for a variety of main group and transition metal ions. Our previously reported reductive ring-expansion approach to the concise synthesis of medium-ring bicyclo[5.5.2], [6.5.2], and [6.6.2] tetraamine ligands (general structures 1-3), the "cross-bridged" tetraamines, will be discussed, along with recent improvements and modifications to the route. The utility of particular members of this class of ligands in radiodiagnostic medicine will be discussed. Significant progress has been made in the area of positron emission tomography (PET) imaging of cancer utilizing ^{64}Cu(II) complexes of cross-bridged tetraamines. Recent work on the synthesis of various pendant-arm, selectively N- and C-functionalized, benzo-annelated, and bis-cross-bridged-tetraamine analogs will be presented. Heterobicycles 1-3 are also proton sponges, and our recent work on the synthesis of inside-protonated tricyclic analogs will be discussed.



1 **2** **3**

References:

Wong EH, Weisman, GR, Hill DC, Reed DP, Rogers ME, Condon JS, Fagan MA, Calabrese JC, Lam K-C, Guzei IA, Rheingold AL, *J Am Chem Soc,* 2000; 122, 10561-10572.

Boswell CA, Sun X, Niu W, Weisman GR, Wong EH, Rheingold AL, Anderson CJ, *J Med Chem*, 2004; 47, 1465-1474.

Sprague JE, Peng Y, Sun X, Weisman GR, Wong EH, Achilefu S, Anderson CJ, *Clin Cancer Res*, 2004; 10, 8674-8682.

Woodin KS, Heroux KJ, Boswell CA, Wong EH, Weisman GR, Niu W, Tomellini SA, Anderson CJ, Zakharov LN, Rheingold AL, *Eur J Inorg Chem*, 2005; 4829-4833.

Wadas TJ, Wong EH, Weisman GR, Anderson CJ, *Curr Pharmaceutical Design*, 2007; 13, 3-16.

PROLINE-CATALYZED ASYMMETRIC ALDOL REACTIONS. ENANTIOSELECTIVE TOTAL SYNTHESIS OF BIOLOGICALLY ACTIVE NATURAL PRODUCTS

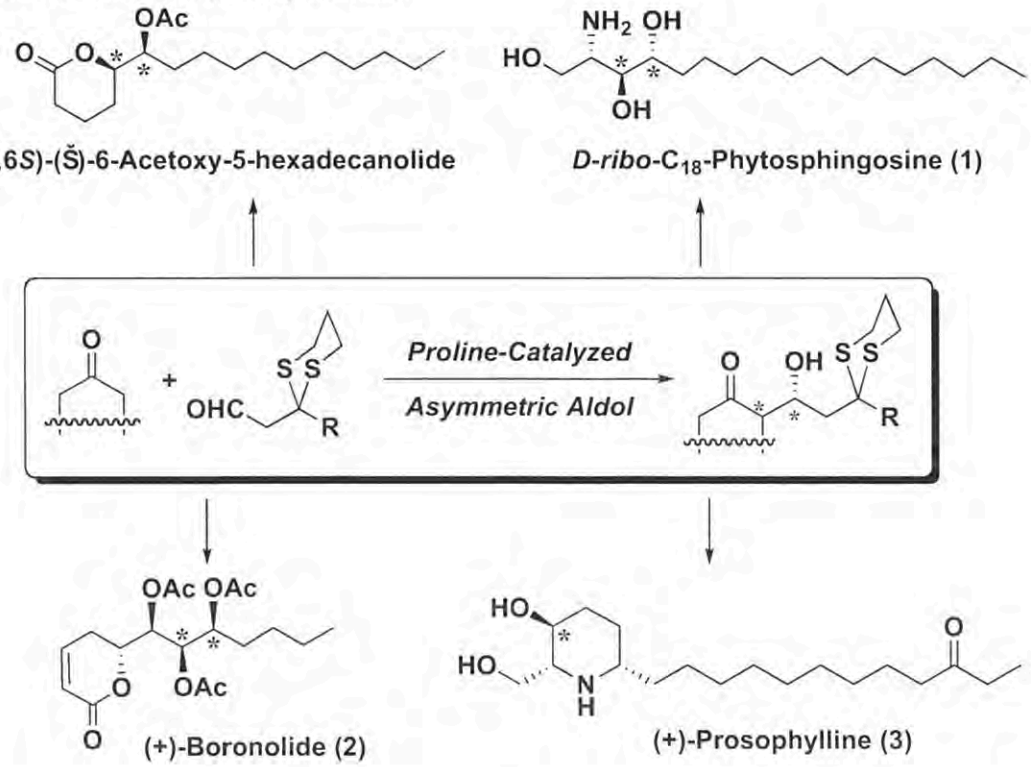
Hideaki IKISHIMA, Atsushi OKUYAMA, Takaaki ISHII, Yoshiyuki ICHINOHE, and Hiyoshizo KOTSUKI*

Laboratory of Natural Product Chemistry, Faculty of Science,
Kochi University, Akebono-cho, Kochi 780-8520, Japan

Recent advances in the field of organocatalytic asymmetric synthesis have provided several new methods for preparing chiral compounds in an environment-friendly manner. Among them, proline-catalyzed asymmetric aldol reactions have been extensively studied due to their great synthetic value. In our recent work on the synthesis of (5*R*,6*S*)-(–)-6-acetoxy-5-hexadecanolide, we found that aldehydes bearing a 1,3-dithiane moiety at the β-position could serve as a useful synthon of straight-chain aliphatic aldehydes [1]. This method was further applied to the enantioselective synthesis of some other biologically interesting natural products as follows.

1. D-*ribo*-C_{18}-Phytosphingosine (1), isolated from the mushroom *Amanita muscaria*.
2. (+)-Boronolide (2), isolated from the bark and branches of *Tetradenia fruticosa*.
3. (+)-Prosophylline (3), isolated from the African mimosa *Prosopis africana* Taub.

The details of these works will be presented.



[1] Ikishima, H; Sekiguchi, Y; Ichikawa, Y; Kotsuki, H. *Tetrahedron* 2006, *62*, 311-316.

NITROHALOALKENES - VALUABLE BUILDING BLOCKS FOR THE DIRECTED SYNTHESIS OF PERSUBSTITUTED HETEROCYCLES

Viktor Zapol'skii and Dieter E. Kaufmann*

Clausthal University of Technology, Institute of Organic Chemistry, Leibnizstr. 6, D-38678 Clausthal-Zellerfeld, Germany. E-mail: dieter.kaufmann@tu-clusthal.de

Due to their stepped reactivity in initial S_NVin reactions, nitro-substituted polyhalogeno-1,3-butadienes have proven to be valuable, synthetic precursors for a variety of polyfunctionalized heterocycles (1-3). Often times the building block of choice is 2-nitroperchloro-1,3-butadiene (1) which is easily accessible by the introduction of an activating nitro substituent into 2H-pentachloro-1,3-butadiene, or benzotriazolyl-activated derivatives of 1. Synthetic use of the versatile building block 1 opens broad access to a quite diverse chemistry, the docu-mentation of which has been started by our group, recently (2).

The preferred primary reaction center of 1 is the partially positively charged terminal carbon atom within the nitrodichlorovinyl moiety. Therefore, this carbon atom allows for a selective attack by different N, O, and S bisnucleophiles. Under harsher conditions the internal carbon atoms C-3 and even C-4 are additionally open to the intramolecular attack of nucleophiles. Thus, a novel high-yield access to 4, 5, 6, and 7-membered heterocycles such as benz-azetines, indoles, pyrazoles, thiophenes, pyrimidines, and diazepinones with an unusual substitution pattern is opened. Both, the mechanisms of these domino reactions and the synthetic potential of the new heterocyclic compounds will be discussed. Many of them show bioactivity, some are interesting building blocks for material science.

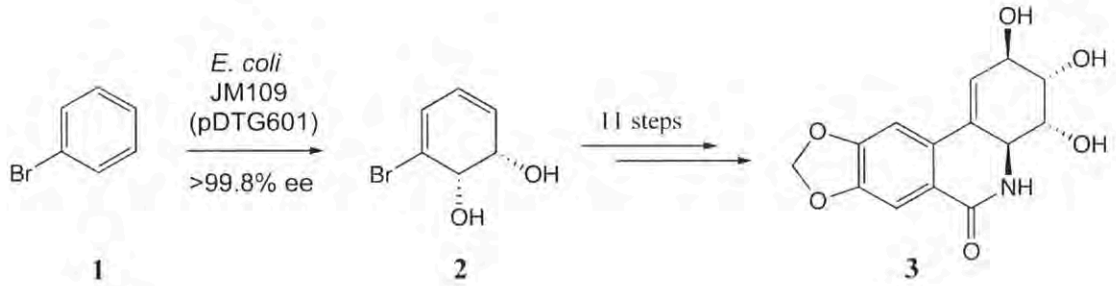
References:
(1) Kaberdin, RV, Potkin, VI, Zapol'skii, VA. *Russ. Chem. Rev.*, 1997; 66, 827.
(2) Zapol'skii, VA, Namyslo, JC, Adam, AE, Kaufmann, DE. *Heterocycles*, 2004; 63, 1281.
(3) Zapol'skii, VA, Namyslo, JC, Blaschkowski, B, Kaufmann, DE. *Synlett*, 2006; 3464.

CHEMOENZYMATIC TOTAL SYNTHESES OF *ent*-LYCORICIDINE AND VARIOUS ANALOGUES FROM BROMOBENZENE

Martin G. Banwell and Maria Matveenko

Research School of Chemistry, Institute of Advanced Studies
The Australian National University, Canberra, ACT 0200, Australia

Certain micro-organisms that over-express dioxygenase-type enzymes can be used for the whole-cell biotransformation of halogenated aromatics into the corresponding *cis*-1,2-dihydrocatechols. The products of such processes are generally obtained in enantiomerically pure form and contain a diverse array of strongly differentiated functionality. As such they represent extraordinarily valuable starting materials for the chemical synthesis. This presentation will detail the use of one such compound, **2**, in a total synthesis of, *inter alia*, the non-natural enantiomeric form, **3**, of the *Amaryllidaceae* alkaloid lycoricidine.



References:

(i) For reviews on methods for generating *cis*-1,2-dihydrocatechols by microbial dihydroxylation of the corresponding aromatics, as well as the synthetic applications of these metabolites, see (a) Hudlicky T, Gonzalez D and Gibson DT, *Aldrichimca Acta*, 1999; 32, 35-62; (b) Banwell MG, Edwards AJ, Harfoot GJ, Jolliffe KA, McLeod MD, McRae KJ, Stewart SG and Vögtle M, *Pure Appl. Chem.*, 2003; 75, 223-229; (c) Johnson RA, *Org. React.*, 2004; 63, 117-264.

(ii) For a review on the synthesis and biological activity of *Amaryllidaceae* alkaloid-type natural products see Rinner U and Hudlicky T, *Synlett*, 2005; 3, 365-387.

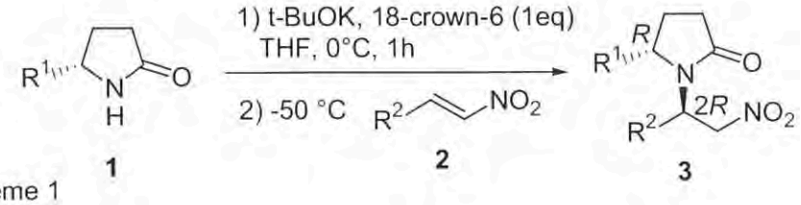
Thursday 19th July
Mathews Theatre A
Contributed Oral Presentations
3:30pm-4:50pm

STEREOSELECTIVE MICHAEL ADDITION OF AMIDES AND LACTAMS TO NITROALKENES

Akio Kamimura,* Yoshiaki Nagata, Ayako Kadowaki, Hidemitsu Uno[+]

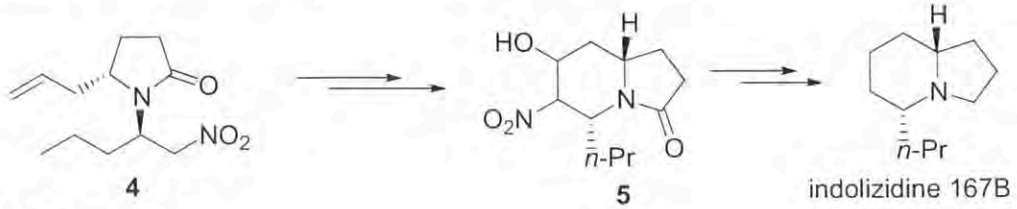
Department of Applied Molecular Bioscience, Graduate School of Medicine, Yamaguchi University, Ube 755-8611 Japan
[+]Integrated Center for Sciences, Ehime University, Matsuyama 790-8577,Japan

The conjugate addition to nitroalkenes is one of the useful reactions to construct carbon backbones in organic synthesis. So far a variety of carbon as well as heteroatom nucleophiles have been utilized for the reaction. Although nitrogen nucleophiles have been sometimes used in the preparation of β-diamines and heterocyclic compounds, β-nitroamines, the adduct of the Michael addition, are relatively labile for handling so that they were used only limited cases. Recently, we have reported formamides works as a good nucleophile to nitroalkenes, and the adducts were prepared in good yields and stable enough for manipulation for further transformation.[1] This method opened a new aspect of nitroalkenes chemistry for heterocyclic synthesis. We examined the conjugate addition of cyclic amide nucleophiles and succeeded to develop stereoselective addition of lactams to nitroalkenes. In this paper we report stereoselective Michael addition pyrrolidinones or piperidinones and its application to synthesis of indolizidine 167B.
The stereoselective Michael addition was performed through the following way: optically active pyrrolidinone 1 was added to a solution of *tert*-BuOK and 18-crown-6 in THF. Nitroalkenes 2 was added to the reaction mixture at -50 °C and the adduct 3 was isolated in good yield. The stereoselectivity of the reaction ranged around 90:10 to 97:3. The addition took place in the absence of 18-crown-6, but the selectivity was spoiled and about 2:1 mixture of the two diastereomers of 3 was obtained. The configuration of C2 was elucidated to be *R* by X-ray crystallographic analysis. The Michael addition to α,β-disubstituted nitroalkenes createed a new stereogenic center at the carbon adjacent to the nitro group, which was readily controlled by kinetic protonation to give the adduct in highly stereoselective manner. A similar selectivity was observed when piperidinoe was employed as the nucleophile for the reaction.



Scheme 1

The present method offered a new formation of bicyclo-heterocyclic compounds. For example, the allyl group in compound 4 was readily converted into aldehyde by treatment of ozone or OsO_4 followed by $NaIO_4$. The aldehyde yielded intramolecular aldol adduct 5 which was promising precursor of indolizidine 167B. We will also report the detail of the conversion.



Scheme 2

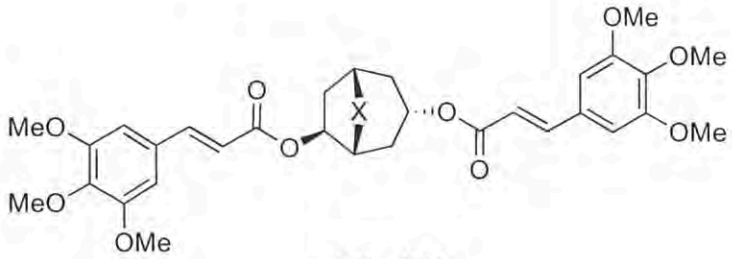
References:
1. Kamimura, A.; Kadowaki, A.; Nagata, Y.; Uno, H. *Tetrahedron Lett.* 2006; *47*, 2471-2473.

THE FIRST ENANTIOSELECTIVE TOTAL SYNTHESIS OF THE PERVILLEINES AND THEIR 8-OXA ANALOGUES, POTENT MDR REVERSAL AGENTS FOR CANCER AND HIV.

Ketav Kulkarni,[a] Patrick Perlmutter[a], Anthony W. Purcell[b] and Anne Y. Zhao[b]

[a] *School of Chemistry, Monash University, PO Box 23, Vic 3800, Australia;* [b] *Department of Biochemistry and Molecular Biology, The Bio21 Molecular Science and Biotechnology Institute, University of Melbourne, 3010 Victoria Australia.*

The Pervilleines are a small family of tropane alkaloids which were recently isolated from the roots of *Erythroxylum pervillei* by Kingsbury et al[1] as part of a screening program for MDR reversal activity in vinblastine-resistant cancer cell lines. In this presentation we will describe the first enantioselective total synthesis of each enantiomer of the most potent of these, namely Pervilleine C (**1**).



1 X = NMe
2 X = O

In addition we have synthesised the 8-oxa-analogues (eg **2**). We have evaluated the performance of each enantiomer of **1** and **2** in MDR cancer cell lines and the results of these studies will also be presented.

References

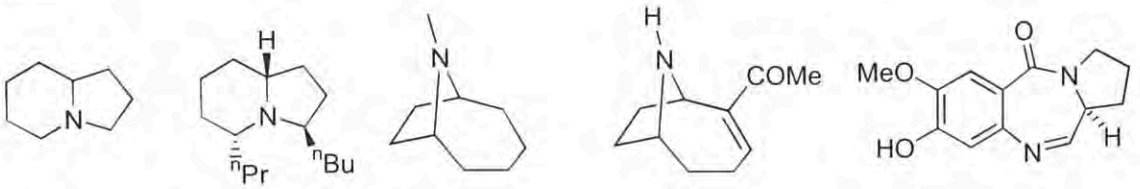
1. Y.-W. Chin, W. P. Jones, T. J. Waybright, T. G. McCloud, P. Rasoanaivo, G. M. Cragg, J. M. Cassady and A. D. Kinghorn *J. Nat. Prod.*, **2006**, *69*, 414-417.

NEW ROUTES TO ANALOGUES OF THE INDOLIZIDINE, HOMOTROPANE AND PYRROLOBENZODIAZEPINE NATURAL PRODUCTS

Paul A. O'Gorman, Nilesh Patel, Chris Chambers, Arnaud Pitard and Karl Hemming*

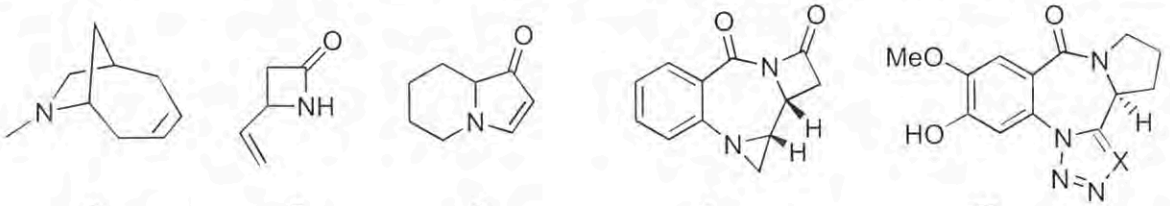
Division of Chemistry, University of Huddersfield, Huddersfield, HD1 3DH, UK.
** email: k.hemming@hud.ac.uk*

The indolizidines 1, such as indolizidine 223AB 2, are attractive targets for synthesis because of the wide range of biological activities that they possess, such as the ability to block nicotinic receptor channels.[1] The homotropanes 3 are a group of alkaloids that includes the natural product anatoxin-a 4, and have attracted attention because of their high affinity for the nicotinic acetylcholine receptor.[2] The third group of natural products that will be detailed in this presentation are the pyrrolobenzodiazepine natural products, such as DC-81 5, and have attracted interest as antitumour antibiotics.[3]



1 **2** **3** **4** **5**

During this presentation, the synthesis of the homotropane isomeric analogue 6 will be described starting from the 1-azetidinone 7 and a cyclopropenone using an aza-Cope rearrangement.[4] The use of cyclopropenones in the synthesis of indolizidines 8 and the related pyrrolizidine and pyrroloazepine nuclei will then be discussed. The use of 1-azetidinones 7 in the synthesis of the novel aziridinobenzodiazepines 9, a process which uses an azide-alkene cycloaddition, will also be presented. A discussion of the synthesis of some other beta-lactam analogues, including some important serine protease inhibitors,[5] will be included. Finally, the synthesis of some pyrrolobenzodiazepine analogues,[6] including the tetracyclic DC-81 analogues 10, will be described.



6 **7** **8** **9** **10**
X = CH or N

References:
1. Daly JW, *Cell. Mol. Neurobiol.* 2005; *25*, 513 – 552.
2. Mansell HL, *Tetrahedron* 1996; *52*, 6025 – 6061.
3. Thurston DE and Bose DS, *Chem. Rev.* 1994; *94*, 433 – 465.
4. O'Gorman PA, Page MI and Hemming K, *Tetrahedron Lett.* 2006; *47*, 425 – 428.
5. Tsang WY, Ahmed N, Harding, LP, Hemming K, Laws AP, and Page MI, *J. Am. Chem. Soc.* 2005; *127*, 8946 – 8947.
6. Hemming K and Patel N, *Tetrahedron Lett.* 2004; *45*, 7553 – 7556.

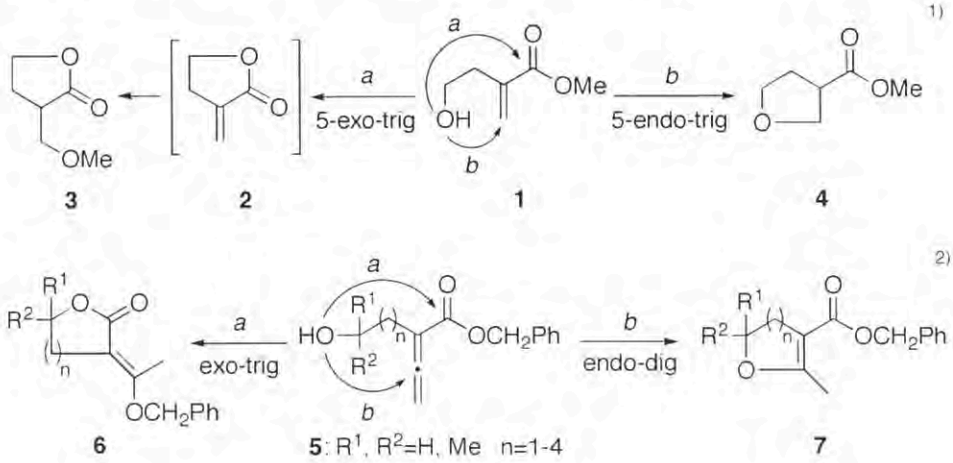
STUDIES OF RING-CLOSING MODE: EXO-TRIG VERSUS ENDO-DIG

Shinji Kitagaki, Daisuke Shibata, and Chisato Mukai*

Division of Pharmaceutical Sciences, Graduate School of Natural Science and Technology, Kanazawa University, Kakuma-machi, Kanazawa 920-1192, Japan

The ring-closing mode, exo- versus endo-manner, sometimes becomes the central issue in the synthesis of target cyclic compounds. The ring-closing mode might be properly predicted on the basis of Baldwin's rule[1a)] that is widely recognized as a reliable empirical rule. As a typical example, the exclusive formation of α-methoxymethyl-γ-lactone **3**, via the reaction of the intermediate of **2** with the liberated methoxide anion, was observed when the αβ-unsaturated-ester compound **1** was exposed to basic conditions.[1b)] This result could be regarded as the so-called "5-exo-trig" mode (route *a*), which is a favored pathway based on Baldwin's rule.[1a)] An alternative "5-endo-trig" mode (a disfavored pathway) leading to compound **4** could not be detected (route *b*).[1b)]

We have investigated the ring-closing reaction of 1-(ω-hydroxyalkyl)-1-(alkoxycarbonyl)allene derivatives **5** under basic conditions to determine if the terminal alkoxide species, generated in situ in the reaction vessel, would preferentially attack the carbonyl functionality through the exo-trig mode (route *a*) or the central carbon atom of the allene moiety through the endo-dig mode(route *b*), both of which are the favored processes according to Baldwin's rule.[1)] We have found that the ring-closing mode (5-exo-trig versus 5-endo-dig) of benzyl 4-hydroxy-2-vinylidenebutanoates **5** (n=1) could precisely be controlled in a highly selective manner by the proper choice of conditions (solvent and base).[2)] One-carbon homologated ester **5** (n=2), however, exclusively afforded the 6-exo-trig mode product **6**. On the other hand, the exclusive formation of seven- and eight-membered oxacycles **7**, via the 7- and 8-endo-dig ring-closing modes respectively, was observed upon treatment of the substrates **5** (n=3,4) having a still longer carbon side chain with a base.



References:
(1) (a) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734–736. (b) Baldwin, J. E.; Cutting, J.; Dupont, W.; Kruse, L.; Silberman, L.; Thomas, R. C. *J. Chem. Soc., Chem. Commun.* **1976**, 736–738.
(2) Kitagaki, S.; Shibata, D.; Mukai, C. *Tetrahedron Lett.* **2007**, *48*, 1735–1738.

Thursday 19th July
Mathews Theatre B
Contributed Oral Presentations
3:30pm-4:50pm

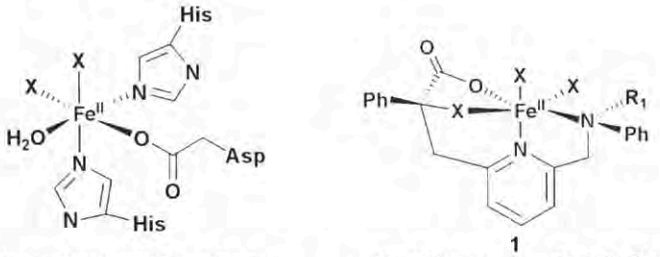
N-HETEROCYCLIC SCAFFOLDS FOR IRON-MEDIATED HYDROCARBON OXIDATION

Barry, S. M., Dungan, V., Wong, S. and Rutledge, P. J.*

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

The efficient and selective oxidation of hydrocarbon substrates is of significant interest in a number of contexts. Converting simple hydrocarbon precursors to functionalised targets cleanly and selectively is of considerable importance in synthetic and medicinal chemistry, while the oxidative breakdown of polycyclic aromatic hydrocarbon pollutants (PAHs, toxic and carcinogenic contaminants) is a key goal in environmental rehabilitation.

Nature uses exquisitely tuned and highly efficient enzyme systems to oxidise hydrocarbons in high yield with complete selectivity. We are working to develop new oxidative reagents inspired by these biological systems as catalysts for hydrocarbon oxidation.

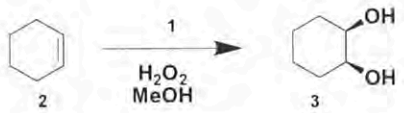


Generalised NHIO Active site

1
X = OH, NH_2; R_1 = Me, Et, Ph

Figure 1

We have made a range of systems of general structure **1**, which are built around a central nitrogen heterocycle and based on the chemistry of the non-heme iron oxidase (NHIO) enzyme family (Figure 1).[1-3] We have recently demonstrated that our first-generation complexes convert cyclohexene **2** to the *cis*-diol product **3** (Scheme 1),[4] a transformation that does not occur in the absence of the biomimetic ligand.



Scheme 1

Recent turnover results and studies to extend the scope and efficiency of this transformation will be presented, along with synthetic approaches to modified 'second generation' scaffolds, and attempts to characterise intermediates in the oxidative reaction cycle.

References:
1. Costas, M., Mehn, M. P., Jensen, M. P.& Que, L. 2004, *Chem. Rev.* 2004, vol. 104, p. 939-986.
2. Hegg, E. L. & Que Jr., L. 1997, *Eur. J. Bioch.* vol. 250, p. 625-629.
3. Que, L.; Ho & R. Y. N. 1996, *Chem. Rev.* vol. 96, p. 2607-2624.
4. Barry, S. M. & Rutledge, P. J. 2007, *Manuscript in preparation.*

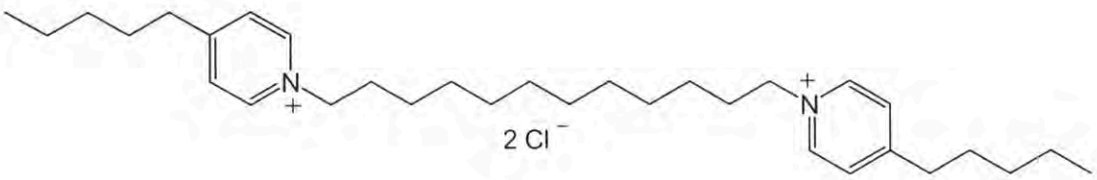
SYNTHESIS AND ANTIFUNGAL ACTIVITY OF BISPYRIDINIUM COMPOUNDS

Obando, D[1]; Widmer, F[2]; Sorrell, T C[2]; Jolliffe, K A[1]

[1]*School of Chemistry, The University of Sydney, 2006, NSW, Australia*
[2]*Centre for Infectious Diseases and Microbiology, Westmead Millennium Institute, The University of Sydney at Westmead, Westmead, 2145, NSW, Australia*

Invasive fungal infections are a serious and escalating health issue. Current therapies are limited in safety and/or efficacy and resistant fungi are an emerging problem. It is widely recognised that new antifungal drugs with a novel mode of action are required.

Fungal phospholipase B (PLB1), which has PLB, lysophospholipase (LPL) and lysophospholipase transacylase (LPTA) activities, is a virulence factor in a number of pathogenic fungi.[1] Using a series of bis-ammonium compounds, we have partly validated this multifunctional enzyme as a new antifungal drug target.[2] Recently we discovered that a bispyridinium compound 1 is active against a range of pathogenic fungi, inhibits fungal PLB1 but not porcine pancreatic PLA_2, and shows very low cytotoxicity by an erythrocyte haemolysis assay.
We have now synthesised analogues of 1 in which the headgroups and linker have been systematically varied. This has allowed us to investigate how structure relates to antifungal activity, fungal PLB1 inhibition and cytotoxicity.



References:
1.Chen S, Wright L, Golding J, Sorrell T. *Biochem. J.*, 2000, 347, 431-439.
2. Ng C, Obando D, Widmer F, Wright L, Sorrell T, Jolliffe KA. *J. Med. Chem.*, 2006, 49, 811-816.

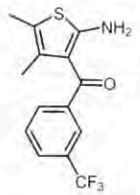
A_1 ADENOSINE RECEPTOR ALLOSTERIC ENHANCERS AS CARDIOPROTECTIVE AGENTS

Gemma N. Ferguson[1], Celine Valant[2], Arthur Christopoulos[2] and Peter J. Scammells[1]

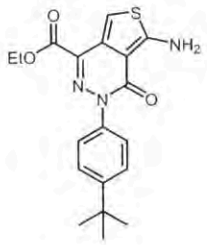
[1]*Department of Medicinal Chemistry, Victorian College of Pharmacy, Monash University*

[2] *Department of Pharmacology, Monash University*

Selective adenosine receptor modulators have the potential for numerous therapeutic applications including cardiovascular, inflammatory and neurodegenerative diseases.[1] Potent and selective adenosine receptor agonist and antagonists have currently been unattainable due to the ubiquitous nature of the adenosine receptor, which leads to a multitude of side effects.[1] A promising area of research is allosteric modulators that utilises the natural levels of endogenous adenosine or exogenous molecules, modulating receptor activity producing effects which would be site and event specific. QSAR analysis of current allosteric enhancers (AEs), including the benchmark compound PD81, 723[2,3] (AE Score 19 %), was performed[4] and identified ethyl 5-amino-3-(4-*tert*-butylphenyl)-4-oxo-3,4-dihydrothieno[3,4-d]pyridazine-1-carboxylate (**1**) as a new lead compound (AE Score 90 %).



PD 81,723



1

Based on this lead compound various derivatives have been synthesised and biologically assayed for allosteric enhancement and antagonism of hA_1AR. Some of these derivatives have found to be specific in their activity with a few of them showing both AE and antagonism of the A_1AR. However, importantly the AE and antagonism of A_1AR can be separated. Aromatic substituents of the phenyl group are required for AE activity but not necessary for antagonism of A_1AR. In addition it was found that simple saponification of the pyridazine ester increases AE activity and significantly reduces antagonism. Potent inverse agonist and antagonists of the A_1AR have also been found from this study. Our current progress will be discussed further in this presentation.

References:

1. Jacobson, KA, Gao, ZG, *Nat. Rev. Drug Discovery*, 2006; 5, 247-264
2. Bruns, RF, Fergus, JH, *Mol. Pharmacol.*, 1990; 38, 939-949
3. Bruns, RF, Fergus, JH, Coughenour, LL, Courtland, GG, Pugsley, TA, Dodd, JH, Tinney, FJ, *Mol. Pharmacol.*, 1990; 38, 950-958.
4. Horne, J, Chalmers, DK, personal communication.

ABSOLUTE CONFIGURATION OF HETEROCYCLIC NATURAL PRODUCTS BY VIBRATIONAL CIRCULAR DICHROISM

Pedro Joseph-Nathan

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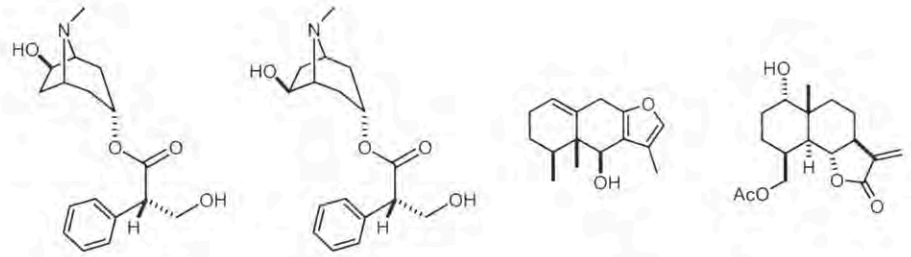
Vibrational circular dichroism (VCD) is an emerging spectroscopic method that is gaining terrain for the absolute configuration determination of organic molecules either isolated from natural sources or derived by synthetic methodology. VCD is a general method (1) in which an optically active measurement can be compared to calculations performed using quantum mechanical equations in the ground state of the molecule. The comparison of both results, that of the measured spectrum and that calculated using density functional theory (DFT), directly provides, for molecules of moderate complexity, the absolute configuration of the studied compound and its conformational preference in solution. Thus, it is a method that allows determining the absolute configuration without reference to a rule or to the need of structural correlation.

VCD can be seen as the extension of classical circular dichroism, now also called electronic circular dichroism, from the ultraviolet and visible regions of the electromagnetic spectrum into the infrared region, or alternatively it can be seen as the determination of an optically active infrared spectrum. The main difficulty in measuring VCD spectra resides in the fact that bands being optical active in the infrared region are of very low intensity, in fact ten thousand to hundred thousand times less intense than classical infrared bands, thereby placing great demands on the optical and electronic requirements of an instrument. Associated to this fact is the mercury-cadmium-telluride detector, used in VCD spectrophotometers, which operates at the liquid nitrogen temperature.

Results will be presented that allow highlighting some of the benefits and limitations of this methodology applied to several natural products. These include the distinction (2) of the two diastereoisomers of the tropane alkaloid 6-hydroxyhyosciamine (**1a** and **1b**), the evaluation of the eremophilanolide 6-hydroxyeuriopsin (**2**) and that of the new sesquiterpene lactone **3**, a guaianolide recently isolated from *Mikania campanulata*.

Regarding calculations, it has to be mentioned that a reasonable balance between computer time and accuracy can be settled when the DFT calculations are performed using the hybrid functional B3LYP and the 6-31G(d) or 6-31G(d,p) basis set, although in some cases a more complex functional and higher basis sets could be required. For the herein studied molecules this resulted in some 30-40 h computer time per conformer when using commercial Gaussian 03 software on a PC system operated at 3 GHz with 2 Mb RAM.



1a **1b** **2** **3**

References:
(1) Freedman TB, Cao X, Dukor RK, Nafie LA, *Chirality*, 2003; 15, 743-758.
(2) Muñoz MA, Muñoz O, Joseph-Nathan P. *J. Nat. Prod.*, 2006, 69, 1335-1340.

Thursday 19th July
Mathews Theatre C
Contributed Oral Presentations
3:30pm-4:50pm

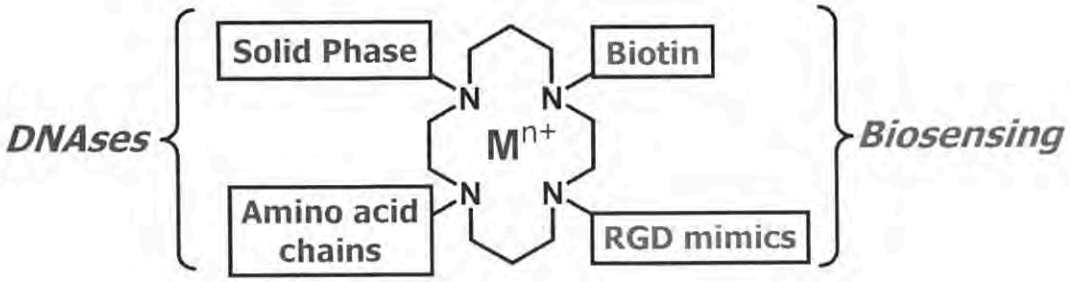
AZAMACROCYCLE COMPLEXES FOR BIOMEDICAL APPLICATIONS

Emiliano Tamanini[a], Sara Krivickas[a], Mike Watkinson[a], Taliesha Paine,[b] A. Venkata Ramana[b] and Matthew H. Todd[b]

a) School of Biological and Chemical Sciences, Queen Mary, University of London, E1 4NS, UK; b) School of Chemistry, University of Sydney, NSW 2006, Australia

E-mail: m.todd@chem.usyd.edu.au

Metal complexes of azamacrocycles offer a remarkably broad synthetic platform for the creation of biomedically interesting molecules. We are exploring this chemistry by generating new complexes for the cleavage and binding of DNA. We have also investigated the attachment of biological ligands and demonstrated the first EPR-based biosensor. The early detection and treatment of cancer may also be possible with straightforward variations on this generic design, accessed by a convergent Click-based synthetic route.

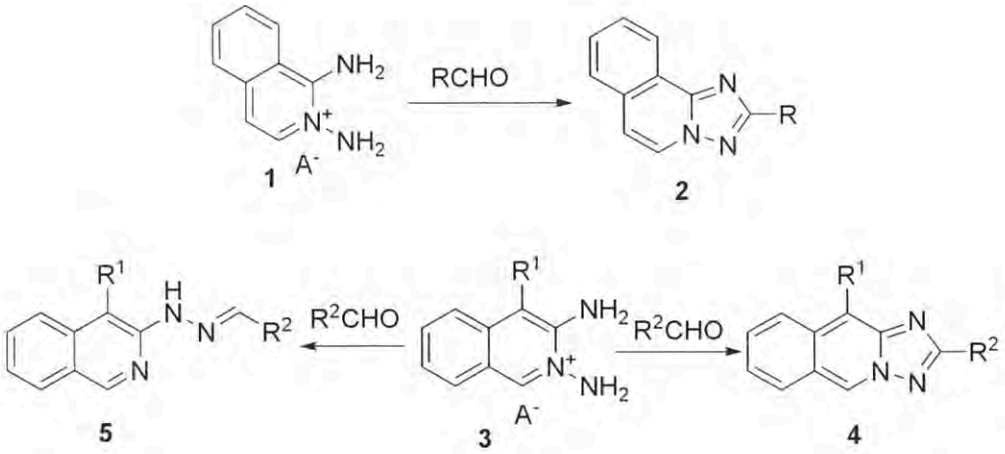


NEW DIMROTH REARRANGEMENT OF AMINOISOQUINOLINIUM SALTS

György Hajós, Zsuzsanna Riedl, László Filák, and Orsolya Egyed

Institute of Biomolecular Chemistry, Chemical Research Center, Hungarian Academy of Sciences, 1025 Budapest, Pusztaszeri út 59-67, Hungary.

Reaction of 1,2-diaminoisoquinolinium salts (1) with various aldehydes in the presence of a base proved to be a general and well applicable approach to the synthesis of [1,2,4]triazolo[3,2-a]isoquinolines (2)[1]. Recent studies on the extension of this ring closure methodology for the isomeric 2,3-diaminoiosoquinolinium (3) salts revealed, however, that although the tricyclic triazole derivatives (4) are also formed in these conversions but, interestingly, 5 hydrazones have been obtained in some cases as revealed by X-ray elucidation and HMBC-NMR experiments.



By application of ^{15}N-labelling technique it has been shown that if R^1 = H or CN, position 1 of the isoquinoline ring can react with a nucleophile being present in the reaction mixture, a Dimroth-rearrangement takes place which gives rise to formation of the hydrazone 5. Clarification of the reaction mechanism allowed that even in those cases where the rearrangement route is favoured, application of proper reaction conditions can lead to conscious direction of the reaction pathway and, also in these cases, the originally intended fused triazoles can be prepared.

Reference:
[1] Hoang, C. N., Riedl, Zs., Tímári, G. Hajós, Gy. Schantl, J. G., *Arkivoc*, ii, 2001, 1060-1070.

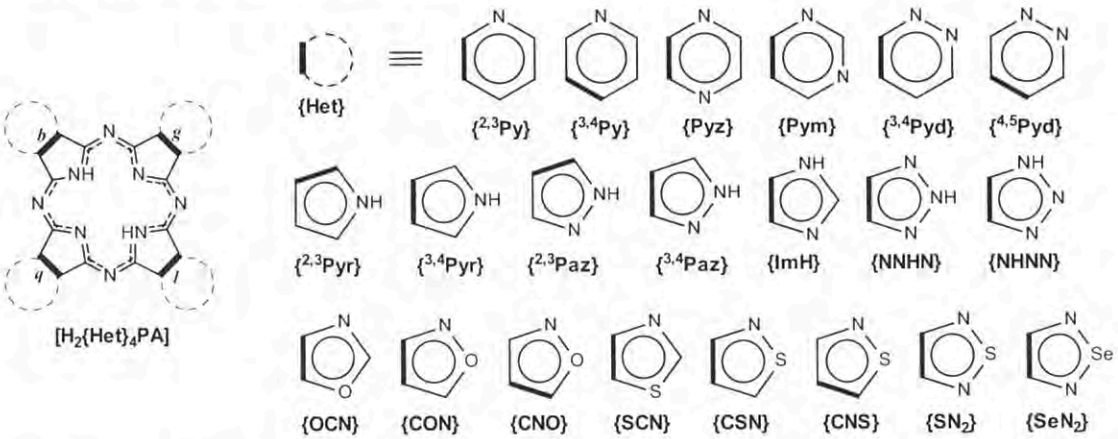
PORPHYRAZINES WITH ANNULATED HETEROCYCLES: THEORETICAL ASPECTS AND EXPERIMENTAL FACTS

Claudio Ercolani[a], Pavel A. Stuzhin[b]

[a]*Dipartimento di Chimica Universita di Roma "La Sapienza", P-le A. Moro, 5, I-00185 Roma Italy, e-mail: claudio.ercolani@uniroma1.it*

[b]Department of Organic Chemistry, Ivanovo State University of Chemical Technology, Friedrich Engels Pr-t, 7, RF-153000 Ivanovo, Russia, e-mail: stuzhin@isuct.ru

Tetrabenzoporphyrazines, commonly named phthalocyanines, have been widely studied due to their numerous useful application properties, unlike their heterocyclic analogues, i.e. porphyrazines with annulated aromatic heterocycles, which remained much less investigated [1]. Among the different classes of porphyrazines, attention was mainly confined, until recent times, to the classes of phthalocyanine analogs carrying peripherally annulated six-membered N-heterocycles (pyridine, pyrazine) and their benzo-derivatives (quinoline, quinoxaline), whereas porphyrazines containing annulated 5-membered heterocycles were not comparably studied.
The results of the theoretical study of the effect of annulation of an aromatic heterocycle to the central porphyrazine core on the geometrical and electronic structure and acid-base properties of this macroheterocyclic system will be presented. It will be shown that in the case of 5-membered heteroarens the position of the heteroatom (NH, O, S) should markedly influence the structure and physico-chemical properties of the macrocycle.



Comparison of the literature and our experimental data with the theoretical results show that annulation of the heteroarens endows porphyrazines with very peculiar and specific structural features and physico-chemical properties in solution and in solid state.
Especially referred to will be porphyrazines carrying annulated 1,2,5-thia/selenodiazole rings intensively studied in our laboratories in the last years [2].

Acknowledgement. PAS is thankful to Russian Foundation of Basic Research for financial support (grants No. 05-03-32921 and 06-03-81022)

References:
1. Stuzhin PA, Ercolani C. Porphyrazines with annulated heterocycles, in *The Porphyrin Handbook*, K.M. Kadish, K.M. Smith, R. Guilard Edrs., Academic Press, Amsterdam, 2003, V. 15, 263-364.
2. Donzello MP, Ercolani C, Stuzhin PA. *Coord. Chem. Rev.*, 2006; 205, 1530-1561

HIGHLY SUBSTITUTED ANTHRACENE BISIMIDE DERIVATIVES: SYNTHESIS AND OPTICAL PROPERITES

Faysal Ilhan,[1] Daniel S. Tyson,[1] and Michael A. Meador[2]

[1]*Polymers Branch, Materials and Structures Division, NASA Glenn Research Center, 21000 Brookpark Road, Cleveland, Ohio 44135 and* [2]*Ohio Aerospace Institute, 22800 Cedar Point Road, Cleveland, Ohio 44142*

Extended aromatic systems, particularly those containing imide and bisimide functionalities, continue to receive considerable attention.[1] Research areas for this general class of organic chromophore include sensors,[2] electron transfer arrays,[3] and liquid crystals.[4] Imides based on naphthalene and perylene have been of particular interest due to synthetic accessibility and useful/tuneable electronic properties. In light of the extensive literature on naphthalene and perylene imides, it is reasonable to expect that anthracene-based imide systems hold potential value. Accounts of anthracene-based imides, however, are limited due to synthetic challenges and limited solubility.[5] A versatile approach to preparing anthracene bisimides would be highly desirable, enabling further investigations of their properties and potential applications.

Recently, we have developed a method for preparing substituted anthracene bisimides based on the well-known process of photoenolization of *o*-methylbenzo-phenones.[5a] In this work, we prepared soluble, highly substituted anthracene bisimides and evaluated their chemosensory behavior. In general, the compounds showed visible absorption (~ 420 nm) and emission (~ 590 nm) with a low quantum yield (~ 0.05) and good photostability in the presence of oxygen. Here we present our current efforts to further investigate these dyes through synthesis and characterization of a systematic series of fluorescent derivatives. The main parameters employed were the degree of functionalization (number of pendant groups) and specific electron donating and/or withdrawing properties. Photophysical studies showed two distinct emitting states, including a π-π^* transition and an intramolecular charge-transfer component. Isolation of the emissive states through synthetic manipulation demonstrated a correlation between the charge-transfer state and the cumulative inductive effects of the substituents.

References:

(1) Hoeben, FJM, Jonkheijm, P, Meijer, EW, Schenning, APHJ. *Chem. Rev.*, 2005, *105*, 1491-1546.
(2) Gunnlaugsson, T, Kruger, PE, Jensen, P, Pfeffer, FM, Hussey, GM. *Tetrahedron Lett.*, 2003, *44*, 8909-13.
(3) (a) Rybtchinski, B, Sinks, LE, Wasielewski, MR. *J. Phys. Chem. A*, 2004, *108*, 7497-7505. (b) Weiss, EA, Sinks, LE, Lukas, AS, Chernick, ET, Ratner, MA, Wasielewski, MR. *J. Phys. Chem. B*, 2004, *108*, 10309-16.
(4) (a) Liu, S-G, Sui, G, Cormier, RA, Leblanc, RM, Gregg, BA. *J. Phys. Chem. B*, 2002, *106*, 1307-15. (b) Müller, GRJ, Meiners, C, Enkelmann, V, Geerts, Y, Mullen, K. *J. Mater. Chem.*, 1998, *8*, 61-64.
(5) (a) Ilhan, F, Tyson, DS, Meador, MA. *Chem. Mater.*, 2004, *16*, 2978-80. (b) Bhattacharyya, S, Toftered, J, Nilsson, UJ. *Synlett*, 2003, *9*, 1361-3. (c) Morris, JL, Becker, CL, Fronczek, FR, Daly, WH, McLaughlin, ML. *J. Org. Chem.*, 1994, *59*, 6484-6. (d) Chiba, T, Kenny, PW, Miller, LL. *J. Org. Chem.*, 1987, *52*, 4327-31.

Thursday 19th July
Mathews Theatre D
Contributed Oral Presentations
3:30pm-4:50pm

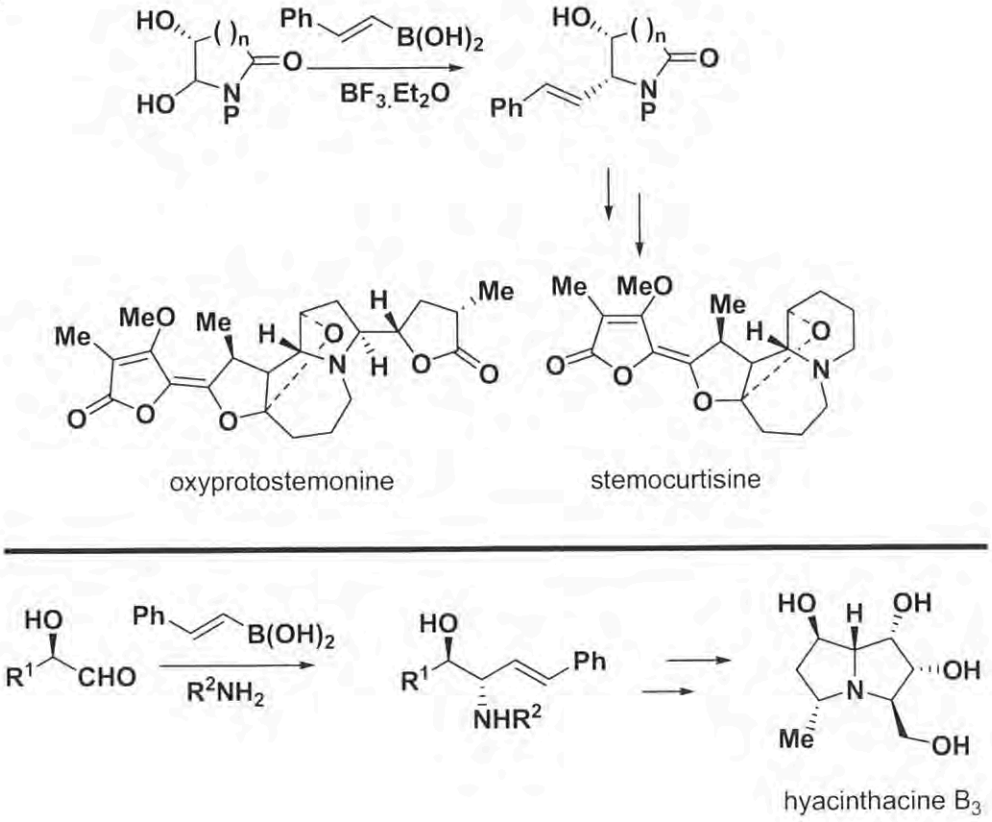
EXPLOITING THE BORONO-MANNICH REACTION IN BIOACTIVE ALKALOID SYNTHESIS

Stephen G. Pyne

Department of Chemistry, University of Wollongong, Wollongong, NSW, 2522, Australia

Progress on the borono-Mannich reaction as a key step in the construction of chiral 5-7-membered ring nitrogen heterocycles will be reported (Scheme 1). The stereochemical outcomes and the mechanism of these reactions will be highlighted and their application to the synthesis of indolizidine, pyrrolizidine and *Stemona* alkaloids will be discussed.

Scheme 1



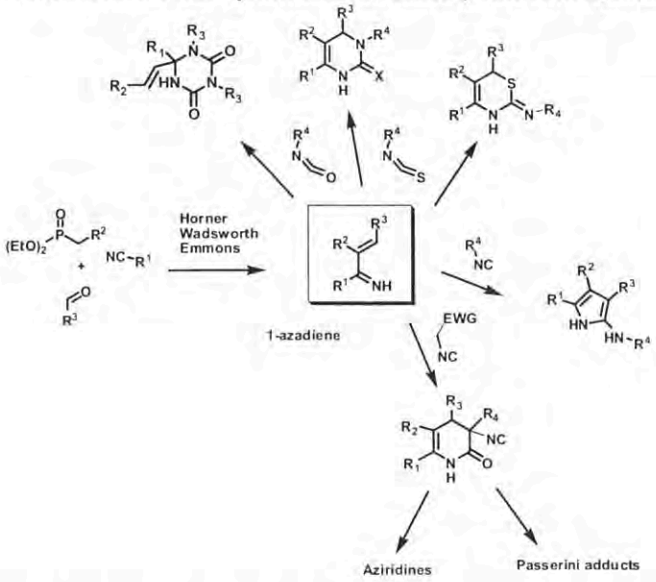
ATOM EFFICIENT AND DIVERSITY ORIENTED MULTICOMPONENT REACTIONS FOR THE SYNTHESIS OF VALUABLE HETEROCYCLES

Romano V.A. Orru, Rachel Scheffelaar, Niels Elders, Monica Paravidino

Department of Chemistry & Pharmaceutical Sciences, Vrije university, Amsterdam The Netherlands, orru@few.vu.nl

Multi-component reactions (MCRs), are one-pot processes that react at least three easily accessible components to form a single product. All atoms of the starting materials are incorporated in the product while the only waste, if any, is water. As such MCRs are well appreciated as tools for the development of novel, clean, and atom efficient procedures for sustainable production of valuable heterocycles. We would like to discuss here novel MCRs to generate structurally complex heterocycles with a maximum of functional diversity that produce a minimum of chemical waste. Structural diversity and complexity are essential to address "drug likeliness" in a ligand, but are also crucial for the design and development of novel ligands for catalyses.

The methodology is based on novel MCRs developed in our laboratory for the parallel synthesis of imidazolines and dihydropyrimidines that possess the required degree of complexity and diversity.[1] We further explored these reactions and would like to present our efforts to combine, *in situ*, an initial MCR with common organic reactions or with a second MCR. Combination of our MCRs with, *e.g.*, cycloadditions, transition-metal mediated cross-coupling or with more traditional MCRs like Biginelli-3CR, Ugi-4CR and the Passerini-3CR will be shown (Scheme). Examples in which the synthetic methodology was applied for the easy generation of focused libraries of N-heterocyclic carbene (NHC) metal complexes as well as for the synthesis medicinally relevant ligands will be discussed.



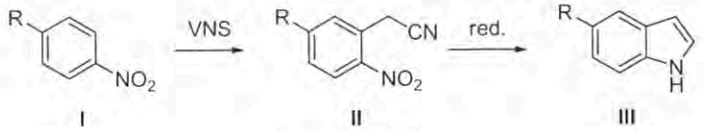
[1] a) Paravidino, M.; Bon, R.S.; Scheffelaar, R.; Vugts, D.J.; Znabet, A.; Kanter, de F.J.J.; Lutz, M.; Spek, A.L.; Groen, M.B.; Orru, R.V.A., *Org. Lett.*. 2006, *8*, 5369. b) Vugts, D.J.; Koningstein, M.M.; Schmitz, R.F.; de Kanter, F.J.J.; Groen, M.B.; Orru, R.V.A., *Chem., Eur. J.* 2006, *7178.* c) Glasnov, T.N.; Vugts, D.J.; Koningstein, M.M.; Desai, B.; Fabian, W.M.F.; Orru, R.V.A.; Kappe, C.O., *QSAR & Comb. Sc.* 2006, *25*, 509. *d)* Bon, R.S.; Vliet van, B.; Sprenkels, N.E.; Schmitz, R.F.; Kanter de, F.J.J.; Stevens, C.V.; Swart, M.; Bickelhaupt, F.M.; Groen, M.B.; Orru, R.V.A., *J. Org. Chem.* 2005, *70, 3542.*

RECENT ADVANCES IN UTILIZATION OF VICARIOUS NUCLEOPHILIC SUBSTITUTION (VNS) PRODUCTS IN THE SYNTHESIS OF INDOLES

Stanislav Radl, Josef Cerny

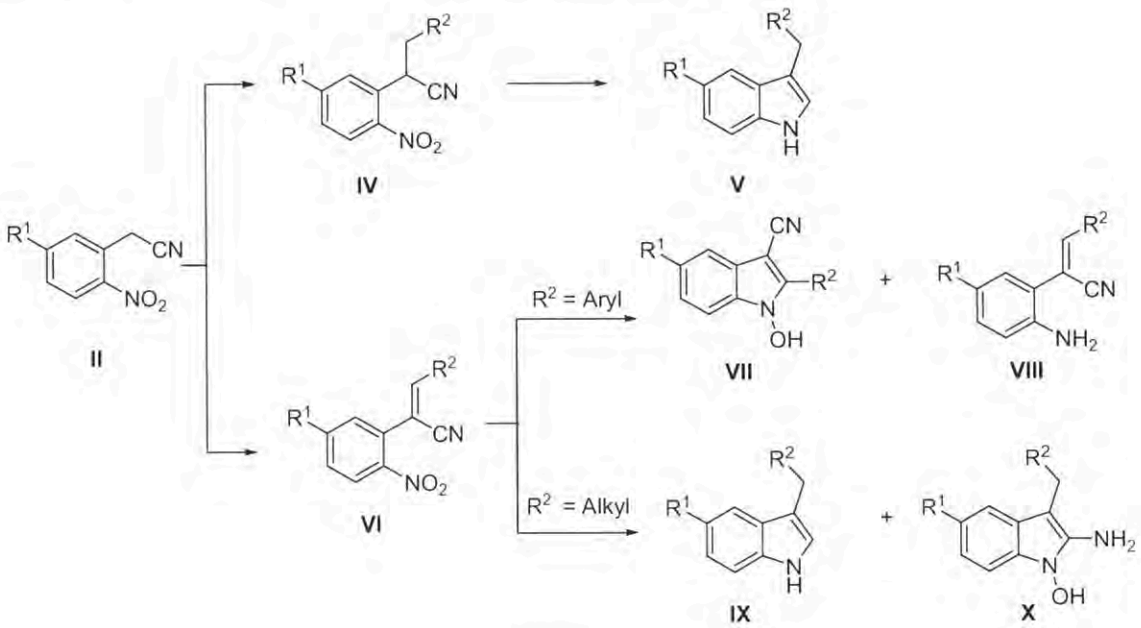
Zentiva – Research Instrituted of Pharmacy and Biochemistry, U kabelovny 130, 102 01 Prague, Czech Republic; *Stanislav.Radl@zentiva.cz*

The VNS of hydrogen has been proven as a tool in the synthesis of various heterocyclic compounds and its use in the indole ring synthesis has been reviewed (1,2). The most useful procedure is based on reductive cyclization of (2-nitrophenyl)acetonitriles II (3,4), compounds known to be available by the VNS (Scheme 1).



SCHEME 1

However, the usefulness of the methodology has been proven only for limited types of substituents. This presentation summarizes our recent results in attempts to widen the scope of this approach. Some examples, showing only the major products, are outlined in Scheme 2. Structural requirements, conditions as well as applicability of the shown reactions will be discussed.



SCHEME 2

References:
(1) Makosza M. *Synthesis* 1991; 103-111.
(2) M. Makosza M, Wojciechowski K. *Heterocycles* 2001; *54*, 445-474.
(3) Stephen H. *J. Chem. Soc.* 1925; 1874-1879.
(4) Walker GN. *J. Am. Chem. Soc.* 1955; *77*, 3844-3850.

HETEROCYCLIC KETENE AMINALS: VERSATILE SYNTHONS FOR THE SYNTHESIS OF NOVEL HETEROCYCLES

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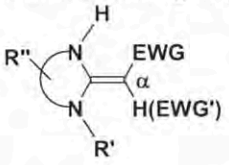
Heterocyclic ketene aminals (HKAs) 1, also referred to as cyclic ketene *N,N*-acetals or cyclic 1,1-enediamines, can be generally depicted by the following formula. These polyfunctionalized heterocyclic compounds are remarkable in that they are very easy to generate from cheap starting materials, reactive to many kinds of reagents and unusually stable at the same time. The combined structural and chemical features of heterocyclic ketene aminals make them powerful synthons for heterocycle synthesis and attracting targets to study.



1

EWG, EWG' = NO_2, CN, COR, CO_2R etc.
R', R'' = H, alkyl, aryl, etc.
Different ring size

Owing to the conjugation effect of the electron-donating secondary amino groups and electron-withdrawing substituent(s), the C=C bond of the HKAs is highly polarized and the electron density on the α-carbon is increased. So both the α-carbon and the secondary amino group can be employed in the reactions with electrophiles. Thus, HKAs can attack not only the electropositive site of electrophiles, even 1,3-dipoles such as azides, nitrile oxides, and nitrile imines, but also can serve as bis-nucleophiles to react with bis-electrophiles to form fused heterocyclic structures by nucleophilic addition or substitution and cyclocondensation sequences. A number of bis-electrophilic reagents, including ethyl bromoacetate, unsaturated carboxylic acid esters and enones, keto esters, 1,3-dibromopropane, diethyl oxomalonate and glyoxylic acid esters, have so far been successfully used in the reactions with HKAs. Therefore, Heterocyclic ketene aminals (HKAs) 1 are powerful synthetic intermediates for the synthesis of a variety of complex fused heterocycles.[1-2]

Herein, we would like to give a brief review on the chemistry of HKAs and to present some of the new reactions we have discovered recently, including reactions with ketene dithioacetals, three-component reactions with aldehydes and active methylene compounds, cascade reactions with some bis-electrophiles, and regio-selective glycosylations, etc. A number of novel heterocyclic structures have been constructed through these reactions (Fig 1).

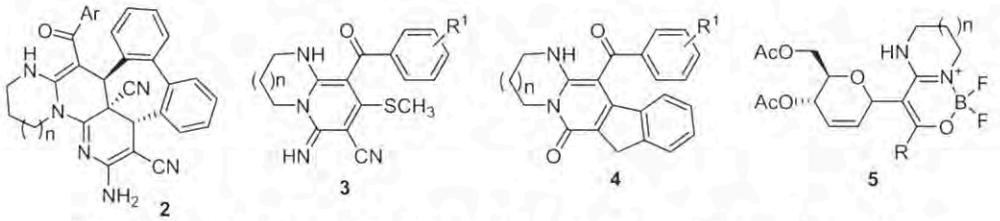


Fig. 1 Examples of novel heterocyclic structures synthesized from HKAs

References:

1. For reviews see: (a) Huang, Z-T; Wang, M-X Heterocycles, 1994, 37, 1233-1262; (b) Huang, Z-T; Wang, M-X. Progress in Natural Science, 2002, 12, 249-257.
2. For our recent work see: (a) Yu, C-Y; Yang, P-H; Zhao, M-X; Huang, Z-T. Synlett 2006, 1835-1840. (a) Liao, J-P; Zhang, T; Yu, C-Y; Huang, Z-T. Synlett, 2007, 761-764.

Friday 20th July
Keynote & Plenary Speaker Abstracts

NEW CYCLOADDITION AND ANNULATION STRATEGIES FOR THE SYNTHESIS OF HETEROCYCLIC COMPOUNDS

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Highly substituted heterocyclic systems are key structural features in many biologically significant and commercially important compounds. This lecture will focus on the application of highly unsaturated, conjugated molecules such as iminoacetonitriles, conjugated enynes, and related species as building blocks for the construction of nitrogen and oxygen heterocyclic compounds. The advantages afforded by benzannulation and intramolecular cycloaddition strategies will be illustrated with examples of their application in the synthesis of biologically active natural products.

THE COMPLEXITY OF THE RING-CHAIN EQUILIBRIUM OF 1,3-(*X-N*)-HETEROCYCLES

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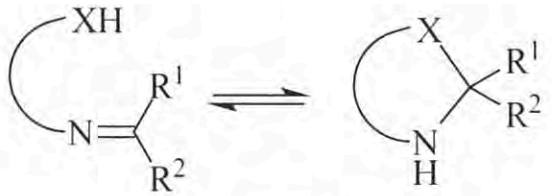
The structures and reactivities of numerous 1,3-*X,N*-heterocycles (X = O, S, NR), where C-2 has an sp^3 character, can be explained, and characterized by the ring-chain tautomeric equilibria, The equilibria involve the intramolecular reversible addition of an XH (X = O, S, NR) group to a C=N double bond to form a cyclic structure. This is often exploited advantageously in different areas of organic synthesis, and also in physical, medicinal and peptide chemistry. The selectivity of certain transformations can be explained on the basis of the ring-chain tautomeric equilibration of the intermediates, followed by a shift in the equilibrium.[1]



X = O, S NR

The present lecture furnishes an overview of recent results on multicomponent *O,N*-heterocycles, and five- and six-membered *N,N*-heterocycles. Up to nine-component tautomeric systems will be discussed. The syntheses of aminobenzylnaphthol derivatives, their transformations to substituted 1,3-diaryl-, 3-alkyl-1-aryl- and 2,4-diarylnaphthoxazines, and studies of the double substituent effects on the ring-chain tautomeric equilibria will also be surveyed.[2,3]

References:

[1] Lázár, L.; Fülöp, F. *Eur. J. Org. Chem.* **2003**, 2999-3024.

[2] Hetényi, A.; Szakonyi, Z.; Klika, K.D.; Pihlaja, K.; Fülöp, F. *J. Org. Chem.* **2003**, *68*, 2175-2182; Zalán, Z.; Hetényi, A., Lázár, L.; Fülöp, F.*Tetrahedron* **2005**, *61*, 5287-5295.

[3] Tóth, D.; Szatmári, I.; Fülöp, F. *Eur. J. Org. Chem.* **2006**, 4664-4669; Szatmári, I.; Tóth, D., Koch, A.; Heydenreich, M.; Kleinpeter, E.; Fülöp, F. *Eur. J. Org. Chem.* **2006**, 4670-4675.

HETEROCYCLES BASED ON THE CHEMISTRY OF ALKYLIDENECYCLOPROPANES AND (AZA-)CYCLOPROPENES

Shengming Ma[1]

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, P. R. China

Alkylidenecyclopropanes, cyclopropenes, and aza-cyclopropenes can be considered as "equivalent" of allenes. Since allenes have been demonstrated to be powerful starting materials for the efficient synthesis of heterocycles,[1] we started to show interest to develop new methods for the synthesis of heterocycles from these three classes of cyclic compounds. In this lecture, we will discuss the transition metal,[2,3] nucleophile,[3-7] or electrophile[8,9] triggered ring opening reactions of these compounds, which lead to the controlled synthesis of heterocycles with new structural features.

References

1. R. C. Zimmer, U. Dinesh, E. Nandanan, F. A. Khan, *Chem. Rev.* **2000**, *100*, 3067. N. Krause, A. S. K. Hashmi, Eds. *Modern Allene Chemistry*, Vols 1-2, Wiley-VCH, Weinheim, 2004. S. Ma, *Chem. Rev.* **2005**, *105*, 2829 and references cited therein.
2. S. Ma, J. Zhang, *Angew. Chem. Int. Ed.*, **2003**, *42*, 183. S. Ma.; L. Lu, J. Zhang, *J. Am. Chem. Soc.* **2004**, *126*, 9645.
3. S. Ma. J. Zhang, *J. Am. Chem. Soc.* **2003**, *125*, 12386.
4. S. Ma, J. Zhang, L, Lu, X. Jin, Y. Cai, Y. Hou, *Chem. Commun.* **2005**, 909.
5. S. Ma, L. Lu, P. Lu *J. Org. Chem.*, **2005**, *70*, 1063.
6. L. Lu, G. Chen, S. Ma, *Org. Lett.*, **2006**, *8*, 835.
7. L. Lu, S. Ma *Eur. J. Org. Chem.*, **2007**, 676.
8. S. Ma, L. Lu *J. Org. Chem.*, **2005**, *70*, 7629.
9. J. Chen, L. Lu, S. Ma to be published.

Acknowledgment. Financial supports from National Natural Science Foundation of China (20121202, 20332060, and 20423001), State Basic and Research Development Program (Grant No. 2006CB806105), and Shanghai Municipal Committee of Science and Technology are greatly appreciated.

THE DIPOLAR CYCLOADDITION ROUTE TO PIPERIDINE ALKALOIDS

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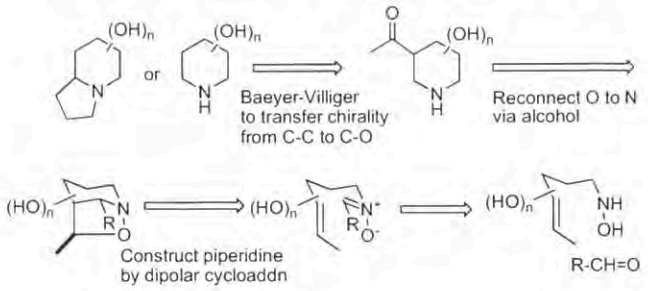
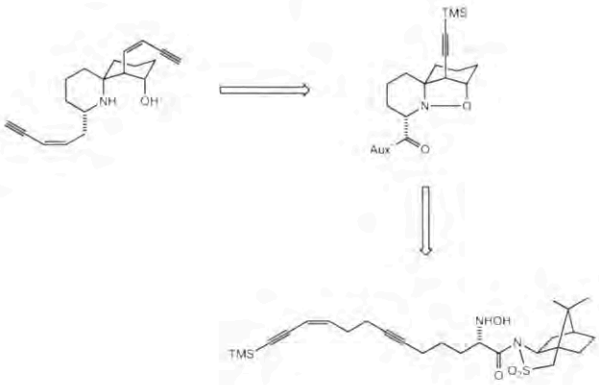
The dipolar cycloaddition of *N*-alkenyl nitrones to alkenes affords isoxazolidines in a stereospecific manner. Reductive cleavage of the *N-O* bond provides 1,3-amino alcohols. The intramolecular variant of this reaction can be used to construct azasugars (Scheme 1).



Scheme 1

In this talk the evolution will be described of a sequential hydroxylamine-alkyne "ene"-cycloaddition in combination with an intramolecular nitrone reaction to produce spirocyclic precursors to the histrionicotoxin family of alkaloids (Scheme 2). The aim was to assemble the histrionicotoxin skeleton from an acyclic precursor carrying a single stereocentre.



Scheme 2

Ultimately this target was realised in a stepwise manner. Recent progress towards the exploitation of a two-directional approach to the histrionicotoxin alkaloids will be described, culminating in a third generation enantioselective synthesis using chiral pool starting materials.

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