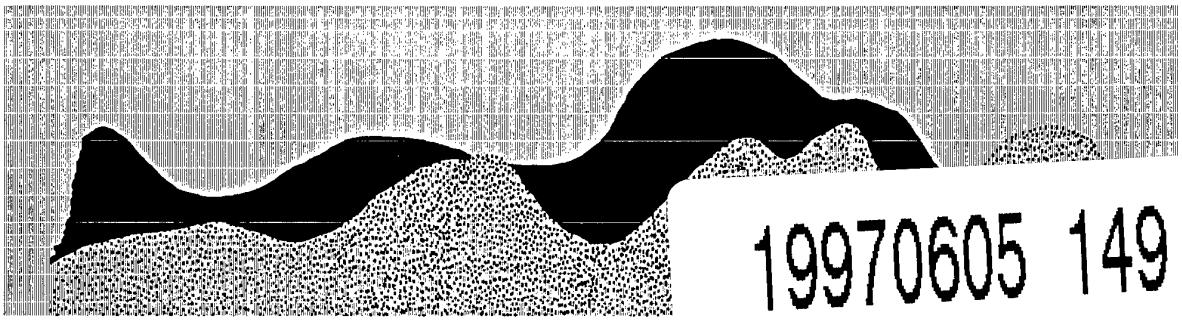
Heterocyclic Group of The Royal Society of Chemistry

Grasmere '97

The Thirteenth Lakeland Symposium on Heterocyclic Chemistry

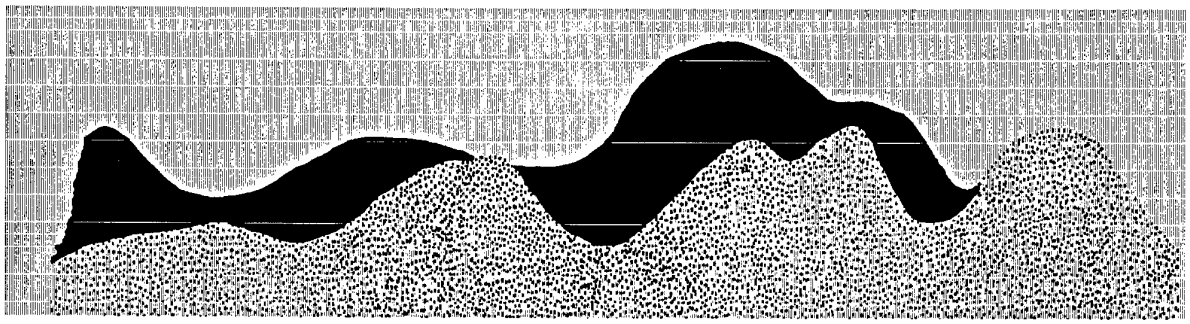


Grasmere Village, Cumbria, UK

8th-12th May, 1997

PRO SCIENTIA ET HUMANITATE

Grasmere '97



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Heterocyclic Group Committee:

Dr K Jones (King's College)
Dr M F Jones (Glaxo-Wellcome)
Dr J Joule (Manchester)
Professor P C B Page(Loughborough)
Professor C A Ramsden (Keele)
Dr F A Sansbury (Organon)

Grasmere Organisers:

Dr K Jones (King's College)
Professor C A Ramsden (Keele)

Grasmere '97

The Thirteenth Lakeland Symposium on Heterocyclic Chemistry

The Heterocyclic Group of the Royal Society of Chemistry is grateful to the following organisations for their generous financial contribution to the support of this meeting:

- Astra Charnwood
  AgrEvo UK
- Avocado Research Chemicals
- British Biotech Pharmaceuticals
- Chiroscience Ltd
- Elsevier
- Glaxo-Wellcome
- Knoll Pharmaceuticals
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- Rhone-Poulenc Rorer
- Roche Products Ltd
- Roussel Scientific Institute
- SB Pharmaceuticals
- US Army European Research Office
- Zeneca Agrochemicals
- Zeneca Pharmaceuticals

The Secretary would also like to thank:

- Mrs Ann Harrison and Mrs Mary Bower (Village Hall)

The hoteliers of Grasmere:

- Mr Robin Lees (Wordsworth Hotel), Mr Roger Benson (Red Lion Hotel), Mr Martin Wood (Moss Grove Hotel), Mr Christopher Carss (Rothay Garden Hotel) and Mr Bob Langman (Harwood Hotel) for their help and cooperation,
- and their staff, for attending to the delegates.

Grasmere '97: 13th Lakeland Heterocyclic Symposium: Summary Timetable

Thursday 8 May

1400-1800	Delegate Registration (Wordsworth Hotel foyer)
1900	*Dinner (meals taken in your own hotel)*
2100	Wine & Beer Mixer (Red Lion Hotel; *vouchers in registration pack*)

Friday 9 May

0800 onwards	*breakfast (check for exact timings in your hotel)*
0910-1045	Scientific Session
1045-1115	*Coffee*
1115-1245	Scientific Session
1300	*Lunch*

afternoon free

17.30-18.00	Discussion on Heterocyclic Group response to Foresight Initiative
1800	*Dinner*
1915-2045	Scientific Session
2100-2300	Poster Session (Wordsworth Hotel, Coleridge Room, *gratis bar*)

Saturday 10 May

0800 onwards	*breakfast (check for exact timings in your hotel)*
0915-1045	Scientific Session
1045-1115	*Coffee*
1115-1245	Scientific Session
1300	*Lunch*

afternoon free

1800	*Dinner*
1915-2100	Scientific Session, including:
2000-2100	Charles Rees Lecture (Professor Al Meyers)

Sunday 11 May

0800 onwards	*breakfast (check for exact timings in your hotel)*
0915-1045	Scientific Session
1045-1115	*Coffee*
1115-1245	Scientific Session
1300	*Lunch*

afternoon free

1900 for 1930	*Conference Banquet (Wordsworth Hotel; tickets in registration pack) (inclusive of wines; bar available for purchase of pre-dinner drinks)*

Monday 12 May

0800 onwards	*breakfast (check for exact timings in your hotel)*
0915-1045	Scientific Session
1045-1115	*Coffee*
1115-1245	Scientific Session
1245-1250	Closing Remarks
1300	*Lunch* (departures during afternoon)

Grasmere '97: TIMETABLE OF SCIENTIFIC PAPERS

Friday 9th May

Morning Chairman: *Professor RJK Taylor*

09.00–09.15 Welcome and Introductory Remarks: *Professor CA Ramsden*

09.15–10.15 ***Professor D H Williams*** *University of Cambridge*
The Action of Vancomycin Group Antibiotics Against "Superbug" Infections

10.15–10.45 ***Professor R C F Jones*** *Open University*
4-Carboxyisoxazoles: Building Blocks for Heterocyclic Tricarbonyl Metabolites

10.45–11.15 COFFEE

11.15–11.45 ***Professor H M R Hoffmann*** *University of Hannover*
Recent Advances in Cinchona Alkaloid Chemistry

11.45–12.15 ***Dr F Heaney*** *University College Galway*
Preparation of Fused Pyrimidine Derivatives: Isoxazolopyrido-pyrimidines, Imidazopyrimidinones and Isoxazolopyrimidodiazepines

12.15–12.45 ***Professor D L Comins*** *North Carolina State University*
Synthesis and Synthetic Utility of 2,3-Dihydro-4-pyridones

LUNCH

Evening Chairman: *Professor CW Rees*

19.15–19.45 ***Dr C M Rayner*** *University of Leeds*
Synthesis and Reactions of New Electrophilic and Nucleophilic Heterocyclic Building Blocks

19.45–20.45 ***Professor A Pfaltz*** *Max-Planck-Institute, Mülheim*
Chiral Oxazolines as Ligands in Asymmetric Catalysis

21.00–23.00 POSTER SESSION IN WORDSWORTH HOTEL
Abstracts listed later in this booklet
(a free bar will operate during the poster session)

Saturday 10th May

Morning Chairman: *Professor H Heaney*

09.15–10.15 ***Professor L Ghosez*** *University of Louvain*
Heterocycles: Targets and Tools in Synthesis

10.15–10.45 ***Professor O Meth-Cohn*** *University of Sunderland*
Synthetic Applications of Umpoled Vilsmeier Reagents

COFFEE

11.15–11.45 ***Dr P O'Brien*** *University of York*
Chiral Base-Mediated Asymmetric Desymmetrisation – A Powerful Tool in Organic Synthesis

11.45–12.45 ***Professor P J Kocienski*** *University of Glasgow*
A Total Synthesis of Salinomycin

LUNCH

Evening Chairman: *Professor CA Ramsden*

19.15–20.00 ***Professor G A Pagani*** *Università di Milano*
Heterocyclic Push-Pull Molecules as Organic Components for Advanced NLO Materials

20.00–21.00 ***Professor A I Meyers*** *Colorado State University*
will deliver the third *"Charles Rees Lecture"*:
Asymmetric Routes to Chiral Heterocycles

Sunday 11th May

Morning Chairman: *Professor MFG Stevens*

09.15–10.15 ***Professor E C Taylor*** *Princeton University*
Novel Inhibitors of Folate-Dependent Enzymes as Antitumor Agents

10.15–10.45 ***Professor J M Bakke*** *Norwegian University of Science and Technology, Trondheim*
A New Nitration Method for Pyridine

COFFEE

11.15–11.45 ***Professor C-K Sha*** *National Tsing Hua University*
Anionic and Radical Cyclisation Approaches to Tetrahydro-3-furanone and 3-Pyrrolidinone: Application to Total Syntheses of Heterocyclic Natural Products

11.45–12.45 ***Professor F A Davis*** *Temple University*
Asymmetric Synthesis and Applications of Heterocycles using Sulfinimines (Thiooxime S-Oxides)

LUNCH

Evening

BANQUET AT WORDSWORTH HOTEL

Monday 12th May

Morning Chairman: *Professor R Westwood*

09.15–09.45 ***Dr T J Donohoe*** *University of Manchester*
The Birch Reduction of Nitrogen-Containing Heterocycles

09.45–10.45 ***Professor A B Smith III*** *University of Pennsylvania*
The Spongistatin (Altohyrtin) Antitumour Agents: Architecturally Complex Synthetic Targets

COFFEE

11.15–12.00 ***Professor A P Johnson*** *University of Leeds*
Recent Developments in Computer-Aided Design of Effect Chemicals

12.00–12.30 ***Professor G W Gribble*** *Dartmouth College*
Novel Indole Chemistry in the Synthesis of Natural Products

Grasmere '97: Poster Session

1. 'Some Applications of Palladium and Cobalt to Heterocycle Synthesis'
   R W Bates, T Rama-Devi and J Ji

2. 'A Radical Approach to the Synthesis of Mitomycins'
   S Brunton and K Jones

3. 'Novel Calix[4]resorcinarene Glycosides'
   A D M Curtis

4. 'A Cycloaddition Route to Heterocyclic Triones'
   C E Dawson, R C F Jones and M O'Mahoney

5. 'An Unexpected Product from the Reactions of 2-Chloro-3-nitrothiophene with 2-Benzylimidazoline'
   R J Hamlyn and C A Ramsden

6. 'A Deconjugation - Alkylation Route to Novel Analgesics'
   S Handa, Q Ong and H Hameyer

7. 'The First Preparation of Episulfones from Episulfides: Oxidation using Oxone®/Trifluoroacetone'
   P Johnson and R J K Taylor

8. 'Heterocyclic Enediynes as Probes of Biomolecule Function'
   G B Jones, J E Mathews, J W Wright and N J Goldspink

9. 'A Radical Route to the Monoterpene Alkaloids Oxerine and Actinidine'
   A Fiumana, **K Jones** and M L Escudero Hernandez

10. 'Alternating π-Electron Deficient: π-Excessive Heteroaromatic Oligomers and Polymers'
    R A Jones, M Karatza, T N Voro, P U Civcir, A Franck, O Ozturk, J P Seaman, A P Whitmore and (the late) D J Wiliamson

11. 'Pyrroloindole Analogues of Ellipticine. The Synthesis and DNA Intercalating Properties of 5,10-Dihydro-5,10-dimethyl-2,5,10-triazabenzo[a,e]pentalene'
    R A Jones, J Bakboord, J Pastor, J Siro and T N Voro

12. 'Trost's Ligand for Palladium (0)-Catalysed Asymmetric Allylic Substitutions'
    I C Lennon

13. 'Approaches to Optically Active N-(2-Aminoethyl)hydroxylamines as Precursors for Heterocyclic Homochiral Nitrones'
    J N Martin and R C F Jones

14. 'A Mild Route to Heterocyclic Acetic Acids Using Sodium Perborate Tetrahydrate'
N Morrow, C A Ramsden, B J Sargent and C D Wallett

15. 'An Unusual Oxidation Reaction with Atmospheric Oxygen: Formation of Piperidines from 1-Azabicyclo[2.2.2]octanes'
T Norris and D Santafianos

16. 'Chiral Base-Mediated Desymmetrisation of Substituted *meso*-Cyclohexene Oxides'
S E deSousa, **P O'Brien** and P Poumellec

17. 'The Nitrile Oxide/Isoxazoline Approach to 3-Deoxy-2-ulosonic Acid Analogues'
P Allen, M B Gravestock, **R M Paton** and C J Todd

18. 'Studies of Novel Nitro-Substituted Nitrogen Heterocycles'
S P Philbin, R W Millar, R G Coombes

19. 'Synthesis of a Novel C2-Symmetric Sulfilimine'
A D M Curtis, R McCague, C A Ramsden and **M R Raza**

20. 'Potential Anthelmintic Compounds based on the Quinoline Alkaloid Atanine'
S Rossiter, K Jones and X Roset

21. 'New Heterocyclic Acyl Anion Equivalents'
R A Aitken and **A W Thomas**

22. 'The Iodobenzene Diacetate Oxidation of Bioactive Phenols'
G Wells and M F G Stevens

23. 'A Tandem Cycloaddition Strategy for the Synthesis of (-)-Histrionicotoxin'
G M Williams and A B Holmes

24. 'The Photochemistry of α-Azidocinnamates - A Reinvestigation'
N J R Williams and O Meth-Cohn

25. 'Synthesis of Indolmycin Analogues with Novel Heteroatom Variation in the 2-Aminooxazolin-4-one Ring'
D R Witty, C L Wayne, D Morris, J Bateson and P O'Hanlon

COMPETITION PROBLEMS

The problems overleaf have been contributed by Professor Malcolm Stevens and his group.

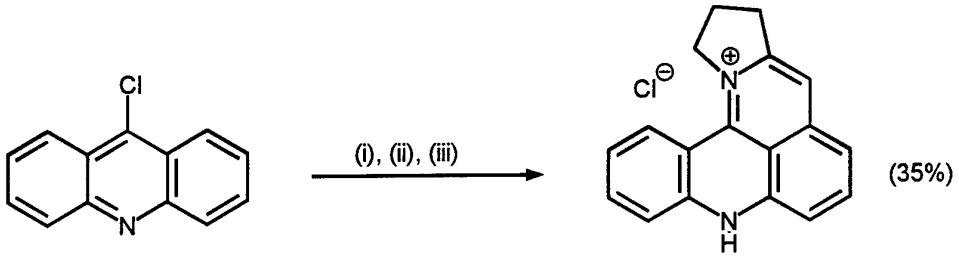
Prizes consisting of bottles of alcoholic beverage will be awarded to the "best" answers as judged by a panel of distinguished heterocyclic chemists. Presentations of prizes will take place at the banquet on Sunday evening.

Answers (carrying your name!) to one of the Group Chairman, Secretary or Professor Stevens by Sunday lunchtime please.

—— THREE PROBLEMS IN ACRIDINE CHEMISTRY ——

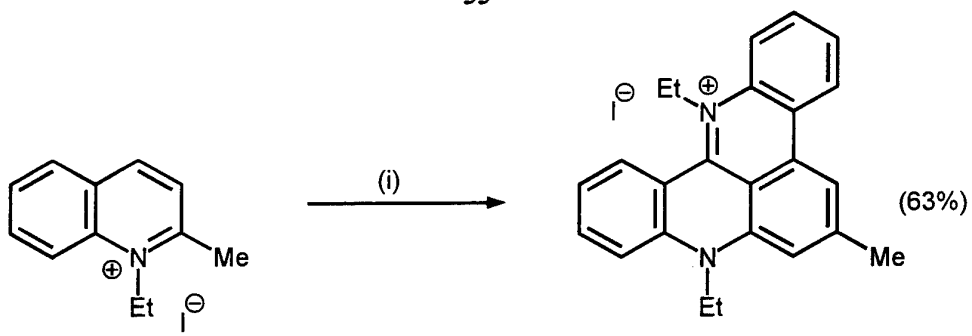
D. J. Hagan, M. F. G. Stevens, M. J. Ellis, and M. Julino*
Cancer Research Laboratories, University of Nottingham, Nottingham NG7 2RD

1. Easy:



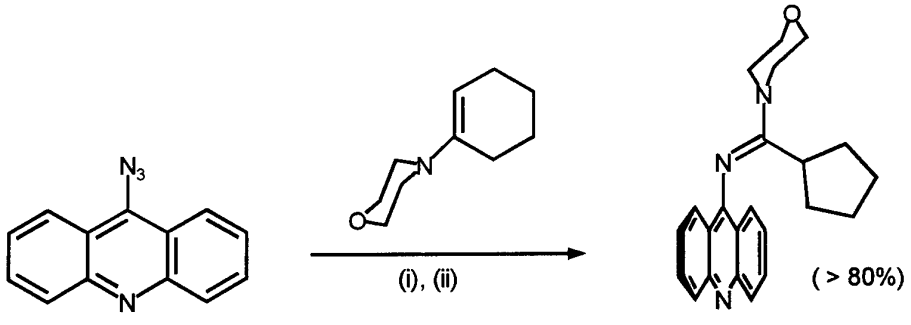
(i) NaN_3 in aq. acetone. (ii) $Cl(CH_2)_3C{\equiv}CH$ at 60°C. (iii) Boiling diphenyl ether (259°C).

2. Difficult:



(i) Piperidine in boiling EtOH (from Oszczapowicz *et al*, *Tetrahedron*, **1988**, *44*, 6645).

3. Quirky:



(i) In CH_2Cl_2 at 25°C. (ii) MeOH at 25°C.

ABSTRACTS

PLENARY LECTURES AND ORAL COMMUNICATIONS

THE ACTION OF VANCOMYCIN GROUP ANTIBIOTICS AGAINST "SUPERBUG" INFECTIONS

Dudley H. Williams

Cambridge Centre for Molecular Recognition,
Department of Chemistry,
Lensfield Road,
University of Cambridge,
Cambridge, CB2 1EW,
UK

The lecture will be an account of the discoveries of the structures and mode of action of the glycopeptide antibiotics of the vancomycin group. These antibiotics are now of enormous clinical importance, for among their members are two (vancomycin and teicoplanin) of the three antibiotics of last resort in our hospitals against resistant bacterial pathogens [particularly methicillin-resistant staphylococcus aureus (MRSA, or "superbugs")], which would otherwise often be lethal. Their combined sales are of the order of U.S. $0.7 billion per annum.

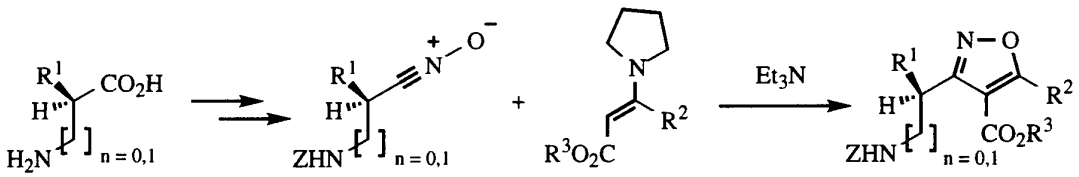
The structures of the glycopeptides will first be described, followed by a brief account of their binding to a bacterial cell-wall peptide precursor terminating in –Lys-D-Ala-D-Ala through the making of 5 hydrogen bonds. In the early 1990s, we established that all the glycopeptides so far examined (other than teicoplanin) form dimers, and shortly after showed that dimerization promotes antibiotic activity. Concurrently, we were able to demonstrate that teicoplanin possesses a membrane anchor which acts to promote antibiotic activity *in lieu* of dimerization. The devices of dimerization and membrane anchoring, when acting concurrently, appear to be able to account for the remarkable activity of a new semi-synthetic glycopeptide - developed at Eli Lilly - against bacteria which are resistant even to vancomycin. A full understanding of these devices is important, since clinicians fear that it is only a matter of time before the molecular feature which is responsible for resistance to vancomycin finds is way into MRSA - a so-called "nightmare scenario".

4-CARBOXYISOXAZOLES: BUILDING BLOCKS FOR HETEROCYCLIC TRICARBONYL METABOLITES

Raymond C F Jones and Claire E Dawson

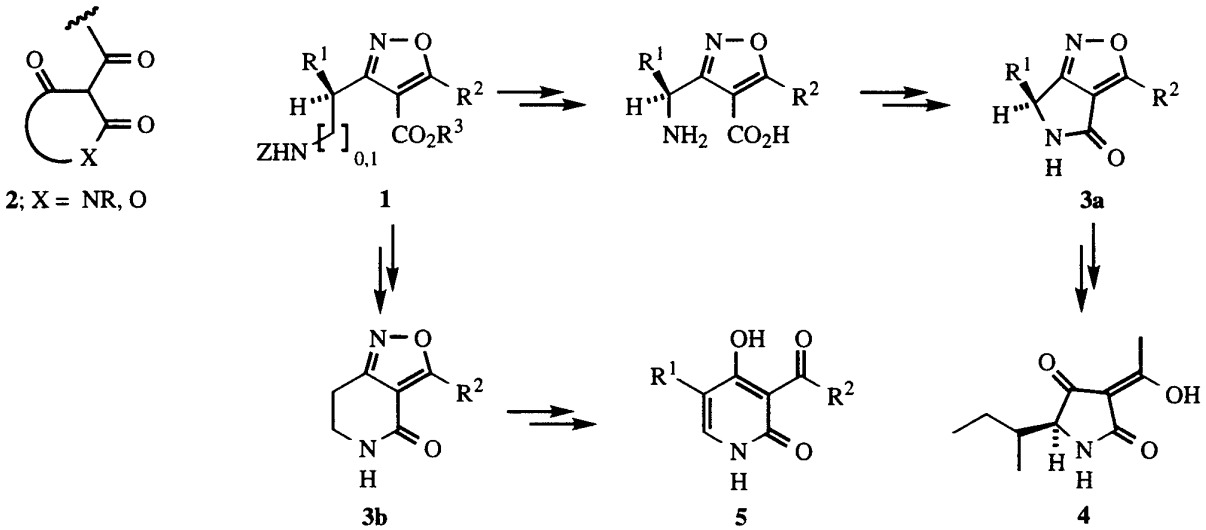
Chemistry Department, The Open University, Walton Hall, Milton Keynes MK7 6AA, UK

We will present some applications of 3-aminoalkyl-4-carboxyisoxazoles **1** in the synthesis of heterocyclic trione natural products. These isoxazoles are prepared by 1,3-dipolar cycloaddition of aminoalkyl nitrile oxides (available from α- or β-amino acids *via* the corresponding amino aldoximes) with the enamines of β-ketoesters.



1

The polar heterocyclic trione system **2** is a constituent of several classes of biologically active natural products. We present applications of the 4-carboxyisoxazoles **1** in a new synthetic methodology towards the *3-acyltetramic acids*, e.g. tenuazonic acid **4**, which shows antibacterial and antiviral activity, and the *3-acyl-4-hydroxypyridone* natural product group **5**, *via* the bicyclic isoxazole-fused lactams **3** as 'masked' non-polar building blocks.



2; X = NR, O

1

3a

3b

5

4

13TH LAKELAND HETEROCYCLIC SYMPOSIUM

GRASMERE, 8-12 MAY 1997

RECENT ADVANCES IN CINCHONA ALKALOID CHEMISTRY

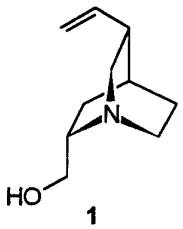
H. M. R. Hoffmann, Department of Organic Chemistry,

University of Hannover, Schneiderberg 1 B, 30167 Hannover, Germany

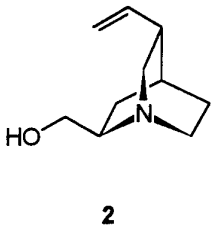
FAX (0511)762-3011, e-mail: hoffmann@mbox.uni-hannover.de

Cinchona alkaloids have served as ligands in asymmetric synthesis and catalysis for some time, while the chemistry of the alkaloids themselves has been studied less.

Recently, we have developed a variety of useful reactions of cinchona alkaloids including the synthesis of novel bicyclic and tricyclic heterocyclic systems. A transformation of quinine and quinidine into functionalized and enantiopure quinuclidines **1** and **2** has been invented[1-3] and put into practice on a multigram scale.



1



2

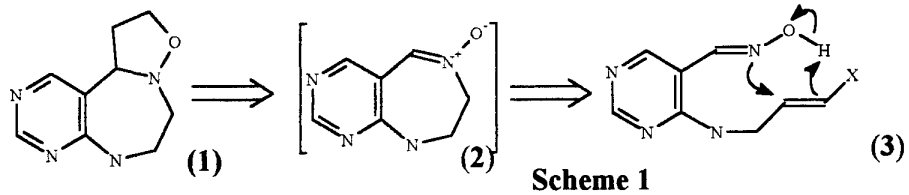
1. H. M. R. Hoffmann, T. Plessner, C. von Riesen, *Synlett* **1996**, 690. German Patent 19604395.6, 7th February, 1996.
2. C. von Riesen, P. G. Jones, H. M. R. Hoffmann, *Chem. Eur. J.* **1996**, *2*, 673.
3. C. von Riesen, H. M. R. Hoffmann, *Chem. Eur. J.* **1996**, *2*, 680.

13TH LAKELAND HETEROCYCLIC SYMPOSIUM
GRASMERE, 8-12 MAY 1997.

PREPARATION OF FUSED PYRIMIDINE DERIVATIVES: ISOXAZOLOPYRIDOPRYIMIDINES, IMIDAZOPYRIMIDINONES AND ISOXAZOLOPYRIMIDODIAZEPINES.

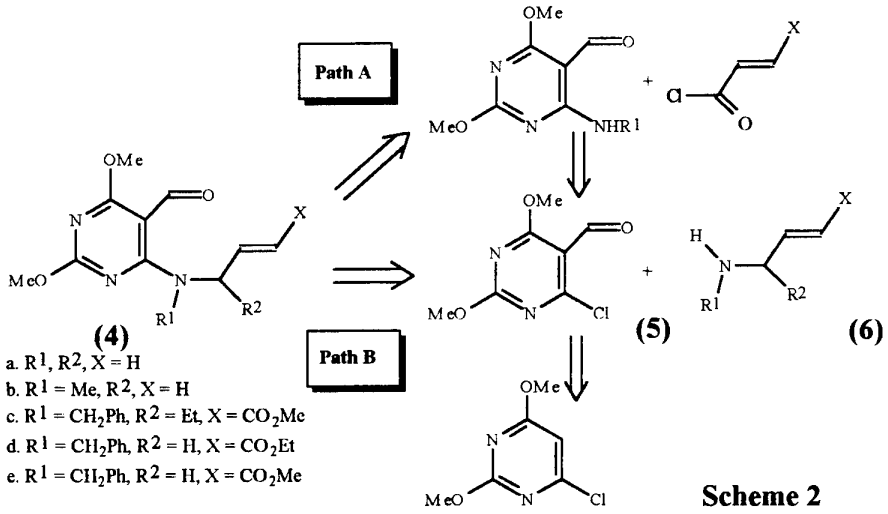
Sharon Bourke, Cathriona Burke and Frances Heaney.
Department of Chemistry, University College, Galway, Ireland.

Our synthetic interest coupled with the biological potential [1] of the isoxazolopyrimidodiazepine ring system directed us toward preparation of systems of the type (**1**). We envisaged (**3**) as an ideal substrate for a tandem dipole formation - cycloaddition reaction (Scheme 1) [2] and accordingly peripherally substituted pyrimidines (**4**) were identified as target starting materials.



Scheme 1

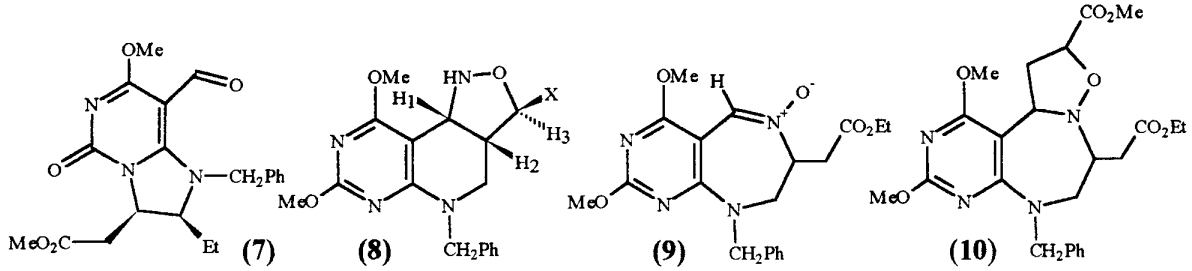
Attempts to prepare the substrates (**4**) from commercially available 6-chloro-2,4-dimethoxypyrimidine [Scheme 2] presented a number of interesting results, in particular when $R^2 \neq H$ instead of the proposed condensation product reaction between the α-formylchloropyrimidine (**5**) and the amine (**6**) lead to the imidazopyrimidinone (**7**).



a. $R^1, R^2, X = H$
b. $R^1 = Me, R^2, X = H$
c. $R^1 = CH_2Ph, R^2 = Et, X = CO_2Me$
d. $R^1 = CH_2Ph, R^2 = H, X = CO_2Et$
e. $R^1 = CH_2Ph, R^2 = H, X = CO_2Me$

Scheme 2

The influence of the substituent X, on the alkene tether of (**4**), in determining the outcome of the reaction of (**4**) with NH_2OH will be discussed; isoxazolopyridopyrimidines (**8**) and/or pyrimidodiazepine *N*-oxides (**9**) may result. The dipole (**9**) can be trapped to give an isoxazolopyrimidodiazepine (**10**), the first example of this tricyclic ring system.



1. Noguchi, M.; Nagata, S.; Kajigaeshi, S. *Chem. Pharm. Bull.*, 1986, 34, 3994.
2. Bourke, S.; Heaney, F., *Tetrahedron Letters*, **1995**, 36, 7527.

SYNTHESIS AND SYNTHETIC UTILITY OF 2,3-DIHYDRO-4-PYRIDONES

Daniel L. Comins
North Carolina State University, Department of Chemistry, Raleigh, NC 27695-8204, USA

Dihydropyridones of the type **1** are interesting heterocycles and attractive building blocks for alkaloid synthesis (Fig. 1). The enone moiety within **1** can be utilized as a Michael acceptor[1], or 1,2-addition to the enone carbonyl can be effected by choosing the proper conditions[2]. The C-5 position of the heterocycle is susceptible to electrophilic substitution[3a], and alkylation at C-3 can be carried out via the enolate[3b]. Due to $A^{(1,3)}$ strain, the C-2 substituent of **1** is forced axial, providing a conformational bias in the molecule[4]. This conformational bias can be used to control the stereochemical outcome of 1,2- and 1,4-additions to the enone as well as alkylations at C-3. In addition to these synthetically useful properties, *N*-acyldihydropyridones **1** are readily prepared in one step by the addition of organometallics to 1-acyl salts of 4-methoxypyridine[1a]. We have reported that dihydropyridones **1** are useful intermediates for the stereoselective preparation of several racemic alkaloids[5]. Recently, we enhanced the scope of this chemistry by describing a method for preparing heterocycles **1** enantiomerically pure by the addition of Grignard reagents[6] or metallo enolates[7] to homochiral 1-acylpyridinium salts. This asymmetric modification has been useful for the enantioselective preparation of various alkaloids[6]. Our latest efforts at expanding the scope of the synthetic utility of these heterocycles will be discussed.

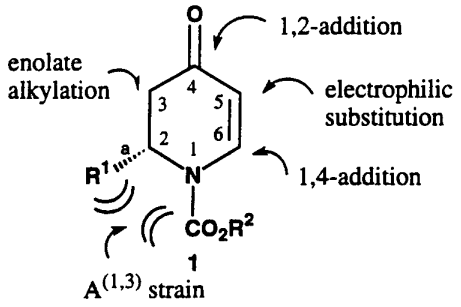


Fig. 1 The versatile *N*-Acyl-2,3-dihydro-4-pyridones

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1. (a) D. L. Comins and J. D. Brown, *Tetrahedron Lett.* **1986**, *27*; 4549; (b) D. L. Comins and M. O. Killpack, *J. Am. Chem. Soc.* **1992**, *114*, 10972 (1992) and references cited therein.

2. (a) Reduction: D. L. Comins, H. Hong and J. M. Salvador, *J. Org. Chem.* **1991**, *56*, 7197; (b) Organocerium reagents undergo preferentially 1,2-addition. D. L. Comins, X. Chen and S. P. Joseph, *Tetrahedron Lett.* **1996**, *37*, 9275.

3. (a) D. L. Comins and L. A. Morgan, *Tetrahedron Lett.* **1991**, *32*, 5919; (b) D. L. Comins and E. Zeller, *Tetrahedron Lett.* **1991**, *32*, 5889.

4. For reviews on $A^{(1,3)}$ strain, see: (a) R. W. Hoffman, *Chem. Rev.* **1989**, *89*, 1841; (b) F. Johnson, *Chem. Rev.* **1968**, *68*, 375.

5. D. L. Comins and R. S. Al-awar, *J. Org. Chem.* **1992**, *57*, 4098 and references cited therein.

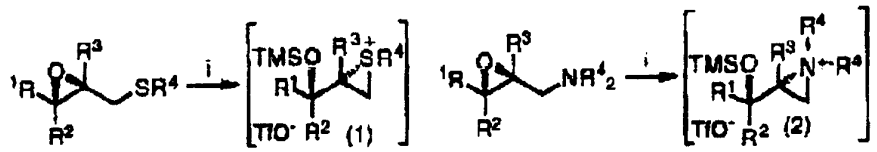
6. (a) D. L. Comins, S. P. Joseph, and R. R. Goehring, *J. Am. Chem. Soc.* **1994**, *116*, 4719. (b) D. L. Comins and Y. Zhang, *J. Am. Chem. Soc.* **1996**, *118*, 12248; (c) D. L. Comins and S. P. Joseph, "Dihydropyridones as Building Blocks for Alkaloid Synthesis," in *Advances in Nitrogen Heterocycles*, Vol. 2, C.J. Moody, Ed., JAI Press, Greenwich, Connecticut, **1996**.

7. (a) D. L. Comins and H. Hong, *J. Am. Chem. Soc.* **1993**, *115*, 8851; (b) D. L. Comins and H. Hong, *J. Org. Chem.* **1993**, *58*, 5035.

SYNTHESIS AND REACTIONS OF NEW ELECTROPHILIC AND NUCLEOPHILIC HETEROCYCLIC BUILDING BLOCKS

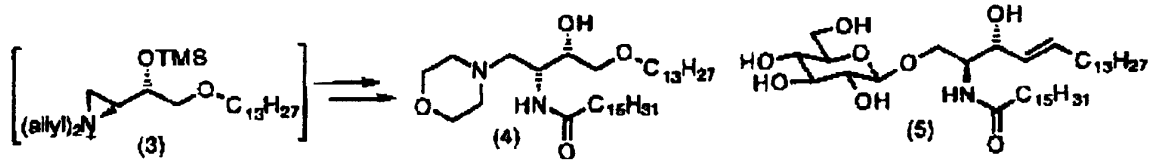
Christopher M. Rayner*[a], Quanying Liu[a], Robert J. Wilson[a], Sandra M. Monaghan[b] and Allan P. Marchington[b]; [a]School of Chemistry, University of Leeds, Leeds LS2 9JT, U.K., email chrisr@chem.leeds.ac.uk; [b]Discovery Chemistry, Pfizer Central Research, Sandwich, Kent, CT13 9NJ, U.K.

We have recently developed efficient methodology for the generation of optically thiiranium ions (1) and aziridinium ions (2), from the corresponding 2,3-epoxy sulfides or 2,3-epoxyamines respectively (scheme 1).[1] These reactive intermediates react efficiently and regiospecifically with nitrogen based nucleophiles, including amines, imines, and amino esters. Application of this methodology for the synthesis of (4), a potential inhibitor of glucosyl ceramide (5) synthase, a possible target for cancer chemotherapy, will be discussed (scheme 2).[2]



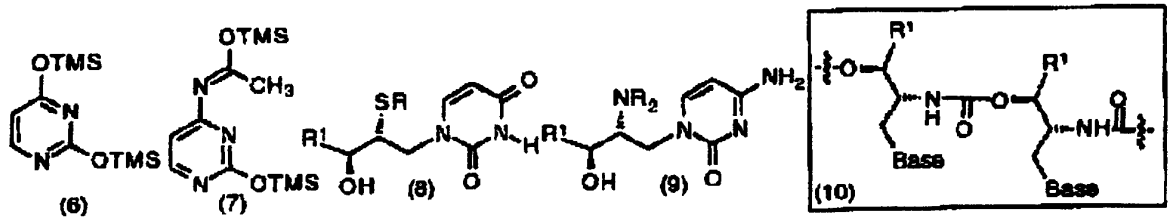
Reagents and conditions: i) TMSOTf, CH_2Cl_2, -78 °C

Scheme 1.



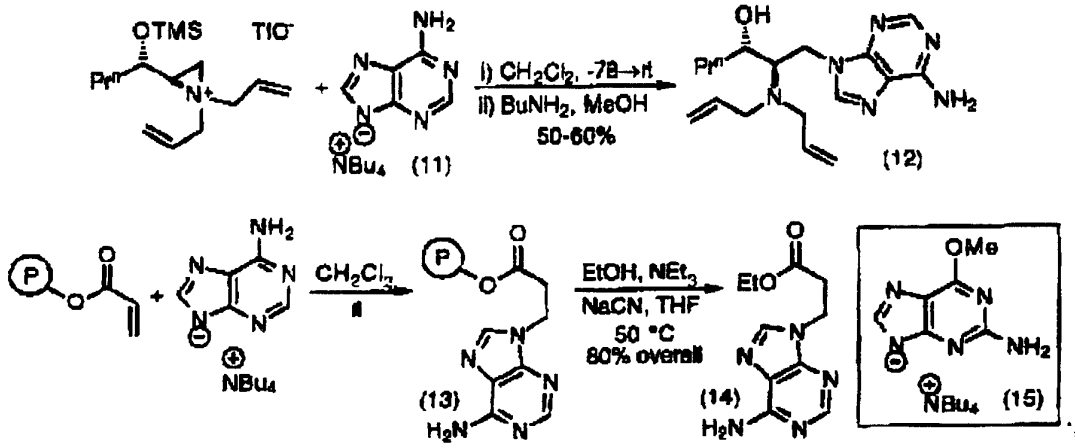
Scheme 2.

As part of a general investigation into the synthesis of novel polymeric systems containing nucleoside bases and other hydrogen bonding groups (e.g. polyurethane 10), we have developed methodology for the reaction of the thiiranium (1) and aziridinium (2) ions with nucleophilic nucleoside base equivalents.[3] We have found that for pyrimidines (e.g. 8 and 9), silylated precursors (6 and 7) react efficiently to give good yields of products as single diastereoisomers and regioisomers.



Scheme 3.

More recently, we have begun to investigate the purine systems, however known silylated or other nucleophilic purine equivalents were unsuccessful, giving only low yields and poor N-9/N-7 regioselectivity. To overcome these problems we have recently synthesised tetraalkyl ammonium salts of purine base equivalents (e.g 11 and 15), which overcome many of the problems previously encountered.[4] These new salts are readily prepared by treating the appropriate purine with a tetraalkylammonium hydroxide, and are generally colourless crystalline solids, soluble in typical organic solvents such as dichloromethane. They also undergo a number of interesting new reactions, including Michael additions to acrylates, both in solution and solid phase (scheme 4). Recent progress in this area will be discussed.



Scheme 4.

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2."Generation of Homochiral Aziridinium Ion Intermediates derived from 2,3-Epoxy Amines: Regiospecific Nucleophilic Trapping with Nitrogen Nucleophiles. Application in the Synthesis of Novel Morpholinosphingolipid Analogues with Potential Glucosyl Synthase Inhibitory Activity", Q. Liu, A.P. Marchington, N. Boden, and C.M. Rayner, *J. Chem. Soc., Perkin Trans. 1*, 1997, 511.

3.D.M. Gill, Q. Liu and C.M. Rayner, unpublished results. See also ref. 1.

4.R.J. Wilson, A.P. Marchington, S.M. Monaghan and C.M. Rayner, unpublished results.

CHIRAL OXAZOLINES AS LIGANDS IN ASYMMETRIC CATALYSIS

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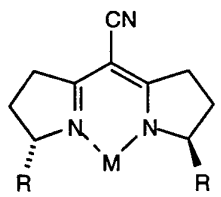
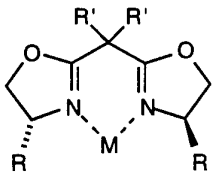
C_2-Symmetric bisoxazolines **2**, which have evolved from our work on chiral semicorrins **1**, are highly effective, versatile ligands for asymmetric catalysis.[1] Copper complexes **2** (M = Cu^I), e.g., have been successfully applied as catalysts for enantioselective cyclopropanation[1] or allylic oxidation of olefins.[2] For a number of metal-catalyzed processes, non-symmetric phosphino-oxazolines or mercapto-oxazolines have proven to be superior to C_2-symmetric bidentate nitrogen ligands. Enantioselective reactions based on catalysts of type **3** (M = Pd, W) or **4** (M = Cu^I) include allylic substitution,[3,4] Heck-type reactions,[5] and 1,4-addition of Grignard reagents to enones.[6] All these ligands are readily prepared in high enantiomeric purity from amino alcohols.



1



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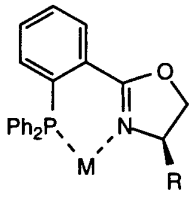

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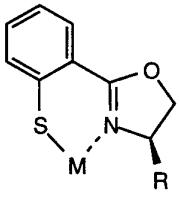

4

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13TH LAKELAND HETEROCYCLIC SYMPOSIUM
GRASMERE, 8-12 MAY 1997

HETEROCYCLES : TARGETS AND TOOLS IN SYNTHESIS

Léon Ghosez
University of Louvain, laboratoire de chimie organique de synthèse, bâtiment Lavoisier, place Louis Pasteur 1, B - 1348 Louvain-la-Neuve (Belgium)

Various types of 2-azadienes have become available from simple building blocks. They react with highly selectivity with a large variety of dienophiles. The lecture will describe new three-component reactions using 2-azadienes as intermediates. The discussion will focus on applications to the synthesis of pyridines, pyrimidines, piperidines, β-hydroxyamides, aminoacids.
The lecture will also discuss a new type of rearrangement allowing the ortho-alkylation of aryl- and heteroaryl acetic acids.

13TH LAKELAND HETEROCYCLIC SYMPOSIUM
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SYNTHETIC APPLICATIONS OF UMPOLED VILSMEIER REAGENTS

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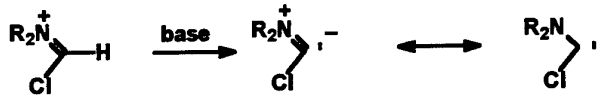
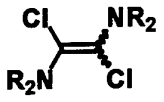
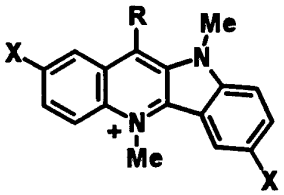
Vilsmeier Reagents (1) are surprisingly acidic molecules and undergo ready deprotonation with tert-nitrogen bases such as Hünig's base or *N*-methylmorpholine to give the nucleophilic

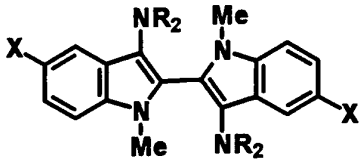


1 2

chloroaminocarbenes (2). This reaction proceeds effectively even in $POCl_3$ solution! The fate of the carbene is dependent upon the conditions of its generation, the base used and the trap available. Thus in THF with Hünig's base high yields of a novel, electron-rich dimer (3) is produced, while in $POCl_3$ solution a trimer (4) is formed with pyridine as the base while aliphatic amines result in a tetramer[1] (5). A one-pot







3 4 5

route from formanilides to isatins will also be described[2] (by way of the dimers 3) as well as further reactions designed to trap the carbenes and to utilise the dimers in synthesis. The mechanism of these intriguing reactions will be explained.

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CHIRAL BASE-MEDIATED ASYMMETRIC DESYMMETRISATION – A POWERFUL TOOL IN ORGANIC SYNTHESIS

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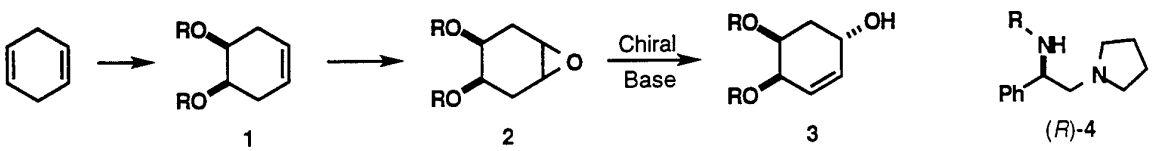
Department of Chemistry, University of York, Heslington, York YO1 5DD UK

New Route to Polyhydroxylated Cyclohexanes – The Strategy

We are currently developing a new, general strategy for the stereocontrolled synthesis of some polyhydroxylated cyclohexanes such as protected deoxy-conduritols **3** (Scheme 1).



Scheme 1: ***The Strategy***

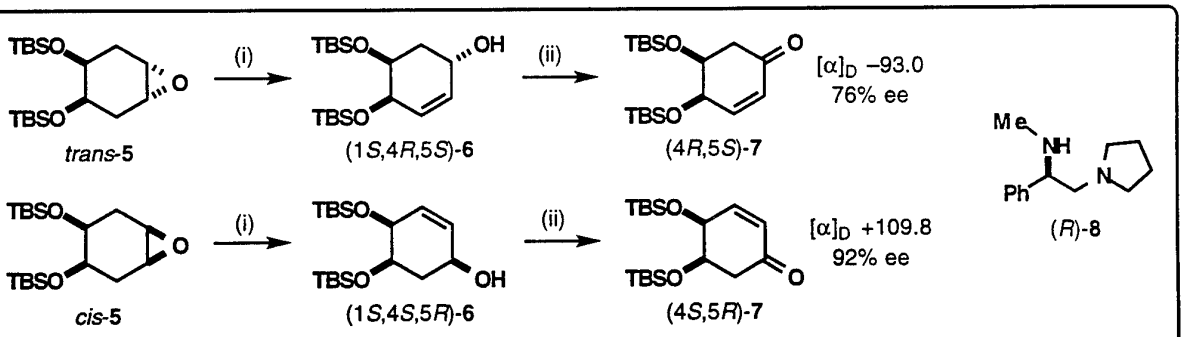
The route starts with achiral 1,4-cyclohexadiene and involves:

- stereospecific introduction of a *cis* 1,2-diol functionality;
- stereoselective epoxidation of **1**;
- enantioselective rearrangement of epoxides **2** to allylic alcohols **3**.

Crucial to the success of our approach is the *asymmetric desymmetrisation* of *meso* epoxides (**2** → **3**); for this, we are using chiral lithium amide bases derived from diamines (*R*)-**4**.

Chiral Base-mediated Rearrangement of Substituted meso*-Cyclohexene Oxides*

In order to test the viability of the strategy delineated in Scheme 1, we prepared both *meso* diastereoisomers of epoxide **5** (using a stereorandom epoxidation reaction) and separately rearranged them using the chiral base derived from diamine (*R*)-**8**. The results are shown in Scheme 2.



Reagents: (i) 1.3 eq (*R*)-**8**, 1.3 eq BuLi, THF, 0 °C → rt; (ii) 1.3 eq PDC, CH_2Cl_2, rt, 4 h

Scheme 2: ***The Strategy Works!***

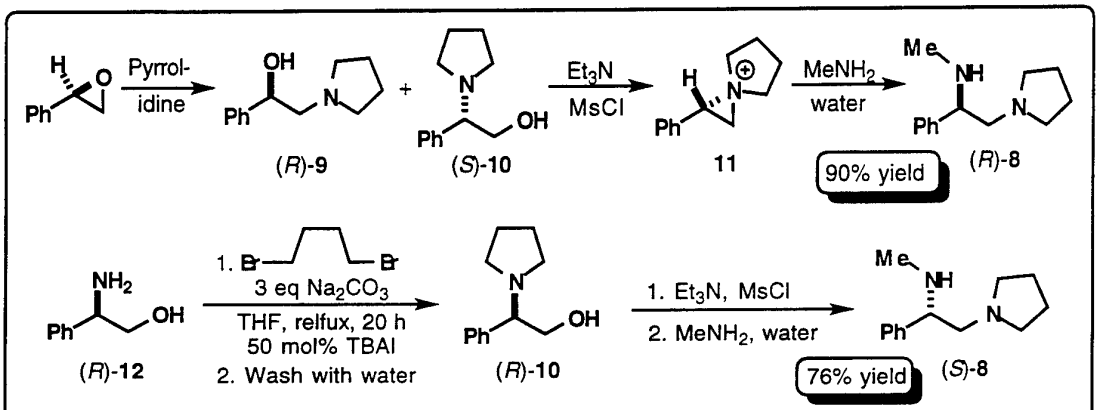
Thus, epoxide *trans*-**5** gave allylic alcohol (1*S*,4*R*,5*S*)-**6** with 76%ee and epoxide *cis*-**5** gave allylic alcohol (1*S*,4*S*,5*R*)-**6** with 92%ee.[1] These results are particularly pleasing for a number of

reasons: (i) this is the first time that these types of substituted *meso* cyclohexene oxides have been rearranged with chiral bases; (ii) the results show that our general strategy works rather well; (iii) oxidation of each of the allylic alcohol products generates a *different* enantiomer of cyclohexenone **7** (even though we used the *same enantiomer of chiral base* in both series).

Two Expedient Methods for the Preparation of Chiral Diamines

As we were clearly going to require significant quantities of chiral diamines **4**, we have developed two new, simple and efficient methods for their preparation. The methods used to make each enantiomer (separately!) of diamine **8** are summarised in Scheme 3.

For example, diamine (*R*)-**8** can be prepared in 90% yield starting from (*R*)-styrene oxide: mesylation of a 70:30 mixture of regioisomers **9** and **10** generates aziridiniun ion **11** which is opened regio- and stereospecifically at the benzylic position by methylamine.[2] This is essentially a *one-pot protocol which is high yielding and technically easy.*



Scheme 3: ***Two Routes to Chiral Diamine 8***

Alternatively, the intermediate amino alcohol **10** from our first route can be prepared via dialkylation of commercially available (*R*)-phenylglycinol **12** using 1,4-dibromobutane in the presence of 50 mol% tetra-n-butyl ammonium iodide (TBAI). The crude product of this alkylation reaction is washed with water to remove the TBAI and then subjected to our usual diamine forming conditions to give diamine (*S*)-**5** in 76% yield over the two steps.[3]

Aziridinium ion **11** has been intercepted by other amines and a variety of chiral diamines have been prepared. Full details will be presented.

References:

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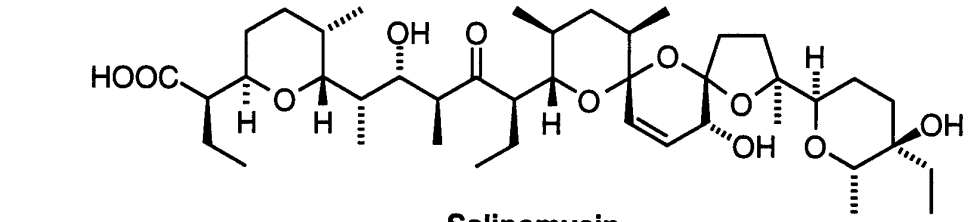
13TH LAKELAND HETEROCYCLIC SYMPOSIUM
GRASMERE, 8-12 MAY, 1997

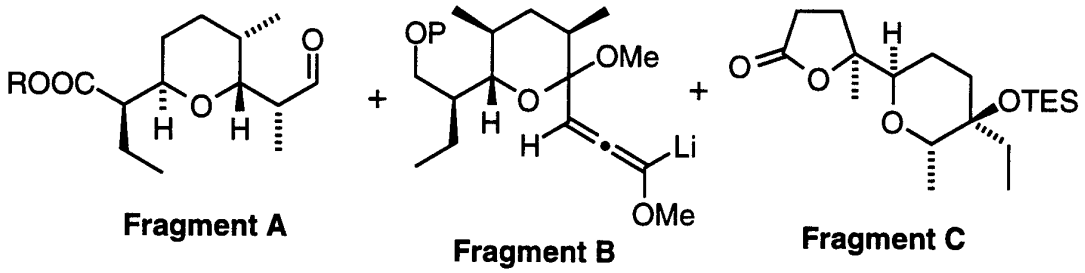
A TOTAL SYNTHESIS OF SALINOMYCIN

Philip Kocienski, Richard Brown, Agnès Pommier, Martin Procter, and Bernd Schmidt
Department of Chemistry, Glasgow University, Glasgow G12 8QQ, UK

A total synthesis of the polyether antibiotic Salinomycin from the fragments A, B and C will be described. The key step in the synthesis of Fragment A is an addition of an α-heteroalkylcuprate to a π-allyl molybdenum cationic complex. The dispiroacetal core is consructed from the metallated allenol ether B and the lactone C. Lactone C is prepared by an asymmetric oxidation of a 1,5-diene in which 4 stereogenic centres are created in a single step.



Salinomycin



Fragment A **Fragment B** **Fragment C**

HETEROCYCLIC PUSH-PULL MOLECULES AS ORGANIC COMPONENTS FOR ADVANCED NLO MATERIALS

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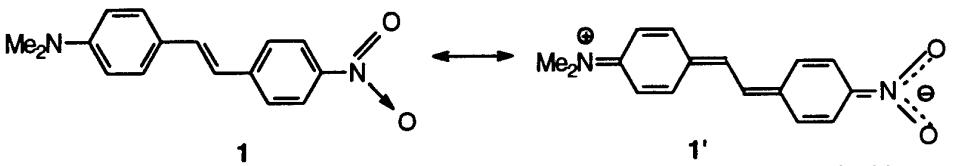
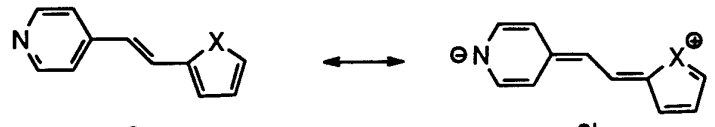
Università di Milano - Dip.to di Scienza dei Materiali - via Emanueli 15 - Milano - Italy

A wide range of applications are responsible for the increasingly greater interest being shown in non linear optic (NLO) materials [1,2], including telecommunications, optical data processing, computing and data storage. Some of these materials have already been marketed [3], but manifacturing companies feel that substantial improvements are needed in order to consolidate and possiibly extend their production. Organic based NLO materials consist of a matrix functionalized by a NLO-phore organic compound which provides NLO activity to the bulk thanks to its polarizability, commonly due to its push-pull nature. 4-Dimethylamino-4'-nitrostilbene DANS (**1**) is the prototype of a large family of 2nd order NLO active systems in which the acceptor and donor units represent primary organic functionalities. Instead, we have used π-excessive and π-deficient heterocycles as donors and acceptors respectively[4]. The investigated compounds of set A are therefore bis-heteroarylvinylogues of DANS. Compounds **3** of set A belong to the rarely investigated class of non-symmetrical dimethine cyanines in which the pyridinium (or azinium) ion is the acceptor, and the five-membered ring (pyrrole, thiophene, indole) the donor.

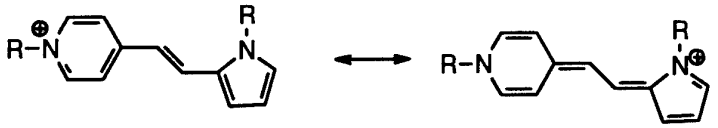


1
ground state: neutral, aromatic

1'
excited state: dipolar, quinoid



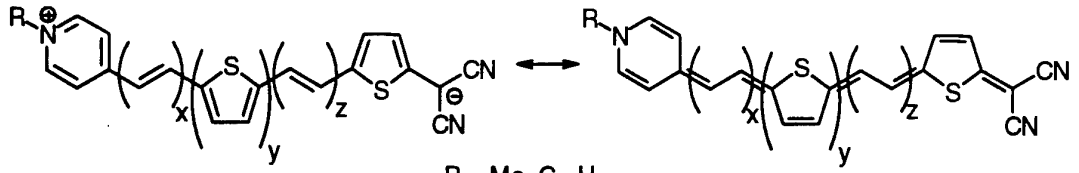
2 **2'**



3 **3'**

Set A

In set B the azinium ion remains the acceptor but the donor becomes a dicyanomethanide unit: spacer groups are either ethylenic or 2,5-thienyl fragments. The association of a dipolar nature with the aromatic structural formalism vs the neutral nature associated with quinoid structural formalism in the compounds of set B is the reverse of that pursued by established push-pull systems of which DANS is the most



R = Me, $C_{16}H_{33}$

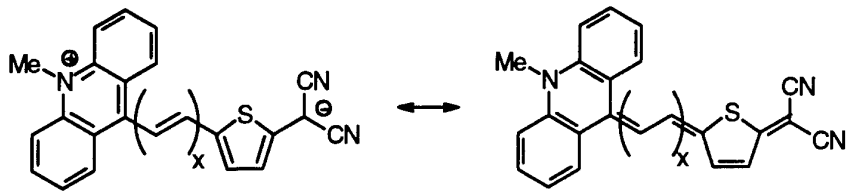
4 ground state: dipolar, aromatic

4' excited state: neutral, quinoid

a: x = y = z = 0; **b**: x = y = 0 z = 1; **c**: x = z = 0; y = 1; **d**: x = 0; y = z = 1; **e** : x = y = z = 1

Set B

representative molecule. We here report the synthesis and characterization of the molecules of sets A and B [4,5]. In order to describe the nature of the ground state of the molecules, we used solvatochromism and NMR indicators as probes to monitor the contribution of the dipolar vs the quinoid structures. The design of the compounds **5** of set C anticipated the result that in these systems the quinoid structure makes a much larger contribution to the ground state than in the molecules **4** of set B.



5 **5'**

a : x = 0; **b** : x = 1

Set C

The dimethine cyanines of set A show high yield processes of two photon pumping [6], which are useful in manipulating laser light. The lower terms of set B present extremely large values of β hyperpolarizability, which are comparable or even better than the best values reported in the literature. The preparation of mixed Langmuir-Blodgett films based on lower cetylated terms of the compounds of set B made it possible to disclose the possibility of using these materials for optical data storage. The pros and cons of these organics in material applications will be discussed.

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[5]. Abbotto, A.; Bradamante, S.; Facchetti, A.; Pagani, G. *J. Org. Chem.* submitted

[6]. He, G.S.; Yuan, L.; Prasad, P. N.; Abbotto, A.; Facchetti, A.; Pagani, G. *Opt. Commun.* in press.

ASYMMETRIC ROUTES TO CHIRAL HETEROCYCLES

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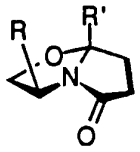
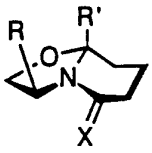
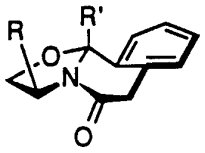
Chiral bicyclic systems (**1-3**) have been readily prepared (some are now commercially available) in high enantiomeric purity and are shown to be highly useful templates to a host of heterocyclic nitrogen systems.



1, R = Ph, *i*-Pr, *t*-Bu
R' = Alkyl, Alkyloxy



2, X = O, S



3

By carrying out a variety of diastereoselective reactions on **1**, **2**, or **3** one can access, in a rather few steps, pyrrolidines, piperidines, isoquinolines, and other systems **all** containing 1-4 stereogenic centers.

In this manner, asymmetric synthetic routes to azasugars, alkaloids, complex tetracyclic natural products (magellanines, conessine) and others have been effectively reached.

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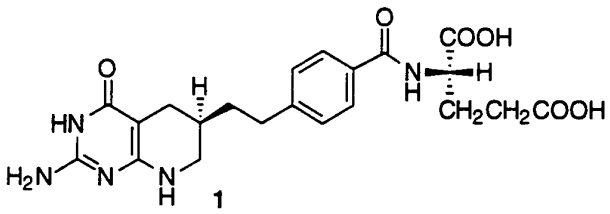
NOVEL INHIBITORS OF FOLATE-DEPENDENT ENZYMES AS ANTITUMOR AGENTS.

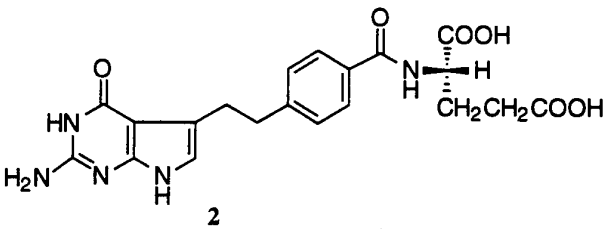
Edward C. Taylor

Department of Chemistry, Princeton University, Princeton, NJ 08544

Folate cofactors are intimately involved in a number of critically important metabolic transformations. For example, 10-formyl-5,6,7,8-tetrahydrofolic acid serves as the cofactor for glycineamide ribonucleotide formyltransferase (GARFT), the first folate-dependent enzyme in the purine biosynthetic pathway which leads, *inter alia*, to GTP and ATP; 5,10-methylene-5,6,7,8-tetrahydrofolic acid serves both as the one-carbon donor and the reducing agent in the methylation of 2'-deoxyuridine-5'-monophosphate (dUMP) to give 2'-deoxythymidine-5'-monophosphate (dTMP) in a process mediated by thymidylate synthase (TS) and which is essential for de novo DNA biosynthesis. We discovered a few years ago that 5,10-dideaza-5,6,7,8-tetrahydrofolic acid (Lometrexol, **1**) inhibited de novo purine biosynthesis as a result of its profound effect on GARFT; this new compound proved to be a potent inhibitor of cell growth and exhibited therapeutic activity against a broad variety of murine solid tumors and human tumor xenografts. We have more recently synthesized a novel multitargeted antifolate and potent antitumor agent (**2**) which inhibits (at nanomolar concentrations) TS, dihydrofolate reductase (DHFR) and GARFT, and (at micromolar concentrations) both aminoimidazole-carboxamide ribonucleotide formyltransferase (AICARFT) and both domains of the C-1 tetrahydrofolate synthetase enzyme. Both of these antifolates are currently in advanced clinical trials for the treatment of solid tumors. This lecture will summarize the design and synthetic studies which led to these new antitumor agents, and a variety of intriguing ring-expanded tetrahydrofolate analogues such as 3-5.



1



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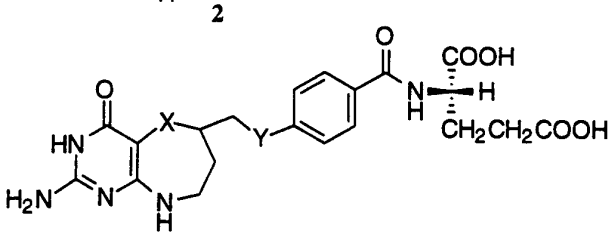

3, X = Y = NH
4, X = NH, Y = CH_2
5, X = Y = CH_2

A NEW NITRATION METHOD FOR PYRIDINE

Jan M. BAKKE

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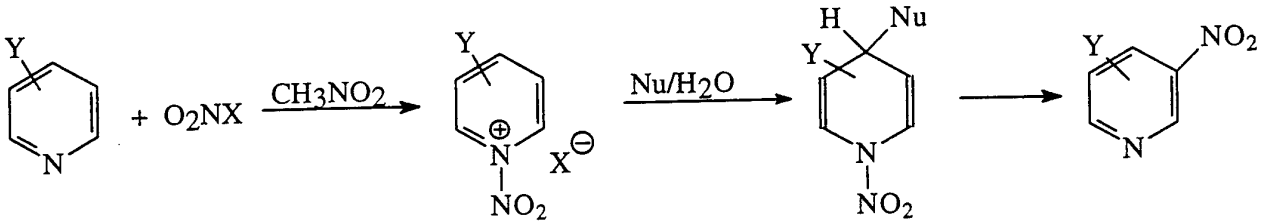
Electrophilic substitution of pyridine takes place only under forcing conditions and often with low yields of substituted products. This is typical so for the nitration of pyridine for which yields in the order of a few percents have been reported.[1] We have recently reported the successful nitration (yields 50 - 70 %) of pyridine and substituted pyridines by the use of dinitrogen pentoxide (N_2O_5, DNP) in liquid sulfur dioxide.[2] We have also discussed possible reaction mechanisms for the reaction.[3]

We now wish to reveal an important new development for this nitration reaction. By this, the use of liquid sulfur dioxide can be avoided and a far better method for the large scale nitration of pyridine compounds is obtained. The pyridine compound is reacted with a nitrating agent, for example DNP or NO_2BF_4 in an organic solvent to form a *N*-nitropyridinium ion (**1**). This is then reacted with an aqueous solution of a nucleophile to give a dihydropyridine complex **2** which reacts to form the β-nitropyridine compound **3**. The results of this reaction and its mechanism will be discussed.



1 **2** **3**

Y = H, CH_3, CH_3CO

20 - 70 %

1. For a summary see Ref. 2 and Scriven, E. F. V. In *Comprehensive Heterocyclic Chemistry,* Vol. 2, Boulton, A. J. and McKillop, A. Eds.; Pergamon: Oxford 1984.
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ANIONIC AND RADICAL CYCLIZATION APPROACHES TO TETRAHYDRO-3-FURANONE AND 3-PYRROLIDINONE: APPLICATION TO TOTAL SYNTHESES OF HETEROCYCLIC NATURAL PRODUCTS

Chin-Kang Sha,* Shih-Jung Huang and An-Wei Hong
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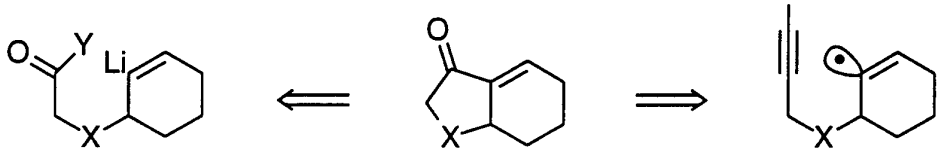
Hsinchu 300, Taiwan, R. O. C.

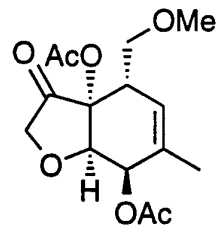
Tetrahydro-3-furanone **1** and 3-pyrrolidinone **2** are potentially useful intermediates for total syntheses of heterocyclic natural products, such as the hexahydrobenzofuran unit **3** of avermectins and haemanthamine **4**. Anionic and radical cyclization approaches toward **1** and **2** have been developed. Their application to the total synthesis of hexahydrobenzofuran unit **3** of avermectins will be presented.



X = O
Y = OEt
N(OMe)Me

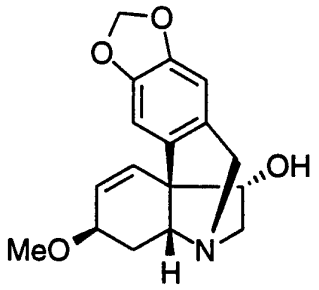
1: X = O
2: X = NR

X = NR



3

Hexahydrobenzofuran unit of Avermectins



4

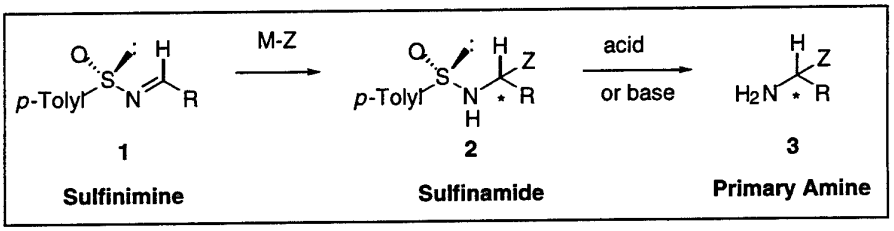
Haemanthamine

ASYMMETRIC SYNTHESIS AND APPLICATIONS OF HETEROCYCLES USING SULFINIMINES (THIOOXIME S-OXIDES)

Franklin A. Davis
Department of Chemistry, Temple University, Philadelphia, PA 19122-2585

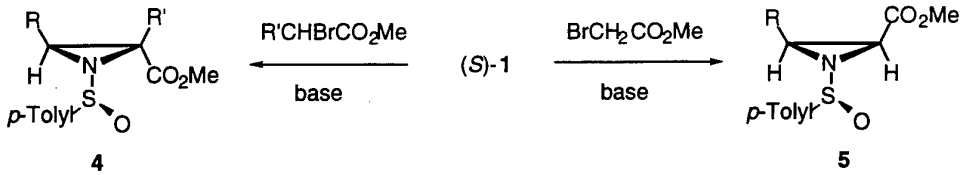
The importance of compounds with nitrogen attached to a stereogenic carbon in biologically and pharmacologically active molecules (amino acids, aziridines, β-lactams, alkaloids, etc.) and their utility as chiral building blocks have stimulated considerable interest in developing practical methods for their synthesis in enantiomerically pure form. Although the diastereoselective addition of organometallic reagents to chiral imines is an attractive route for asymmetric amine synthesis, it is problematic for a number of reasons. First, many nucleophiles fail to react with imines because of their poor electrophilicity. With aliphatic imines enolization is the preferred reaction. Second, stereochemical control is often poor, in part, because imines exist as syn/anti isomers. Some success has been achieved by activation of the imines with Lewis acids and less basic nucleophiles. However, these successes are unique to individual situations.

A more general solution to the problem of imine reactivity and stereoselectivity, developed in our laboratory, employs the sulfinyl chiral auxiliary in sulfinimines (thiooxime S-oxides) **1**. Not only does the sulfinyl group in **1** lead to high de's upon addition of organometallic reagents, but it activates the C-N double bond to such an extent that enolization with aliphatic examples is no longer a significant problem. The product sulfinamide **2**, represents separable diastereoisomers that, on hydrolysis, afford the primary amine derivative without epimerization. An added advantage of the N-sulfinyl group in **2** is that it can be used for further elaboration of the product.

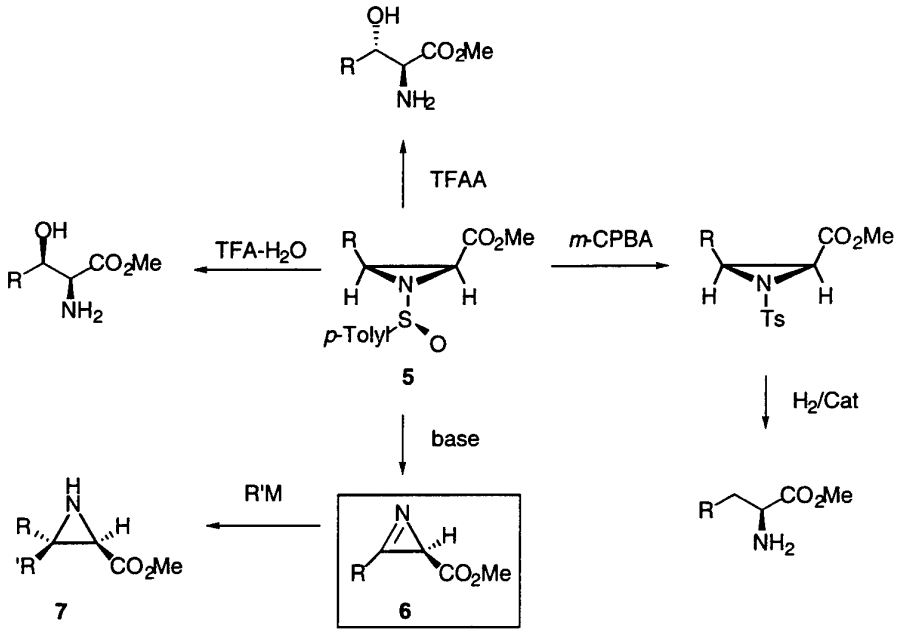


We devised a simple "one pot" procedure for the asymmetric synthesis of sulfinimines **1**, making these compounds readily available for the first time.[1] This protocol involves reaction of lithium bis(hexamethyldisilazane) with commercially available (-)- or (+)-menthyl (*S*)-*p*-toluenesulfinate (Andersen reagent) followed by treatment with an aliphatic or aromatic aldehyde.

Chiral aziridines are versatile intermediates both for asymmetric synthesis and as useful ligands and auxiliaries.[2] Particularly important are aziridine 2-carboxylic acids. By judicious choice of substituents they undergo highly regio- and stereoselective ring-opening reactions with nucleophiles to give β-substituted α-amino acids. Importantly, sulfinimines **1** provide easy access to enantiomerically pure N-sulfinyl aziridine 2-carboxylic acids **4** and **5** by treatment with α-bromo enolates.[3]



Added versatility to the reactions of **4** and **5** is provided by the N-sulfinyl group. For example, oxidation gives the N-Ts derivative, a powerful activating group for aziridine ring-opening.[3a] Aziridine ring opening with retention or inversion of configuration is possible by treatment of **5** with trifluoroacetic anhydride (TFAA) and aqueous trifluoroacetic acid (TFA), respectively.[4] Remarkably, the smallest of the nitrogen unsaturated heterocycles, 2H-azirine 2-carboxylic acids **6**, are available in enantiopure form by reaction of **4** and **5** with base.[5] Addition of organometallic reagents to **6** occurs in a syn stereospecific manner affording the previously unavailable 3,3-unsymmetrical disubstituted aziridine **7**.



Acknowledgments. Our work is supported by the National Institutes of Health, the National Science Foundation and SmithKline Beecham Pharmaceuticals.

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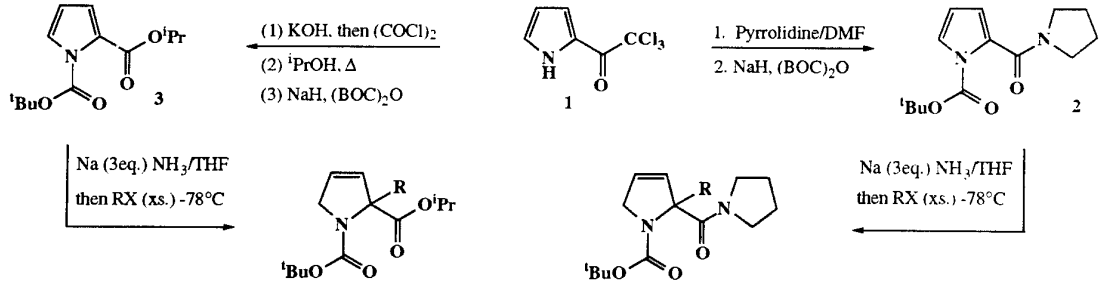
THE BIRCH REDUCTION OF NITROGEN-CONTAINING HETEROCYCLES

Timothy James Donohoe and P. M. Guyo

Department of Chemistry, The University of Manchester, Oxford Road, Manchester, M13 9PL, UK.

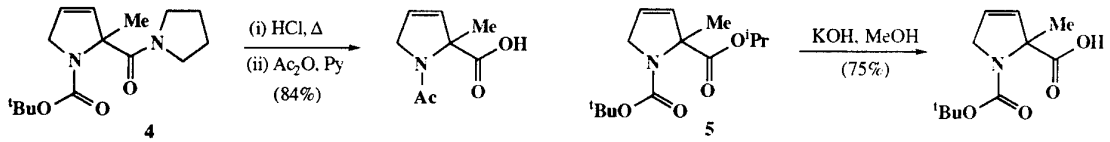
The dissolving metal reduction of aromatic substrates has proven to be a valuable and trustworthy tool in the arena of organic synthesis, capable of bridging between the chemistry of both aromatic and acyclic substrates. Despite the scrutiny that has been turned towards this reduction, exploitation of this reaction to encompass the pyrrole heterocyclic nucleus has been overlooked. We speculated that, in general terms, the pyrrole nucleus was too electron-rich to accept electrons and be reduced. Moreover, the presence of an acidic hydrogen atom on the pyrrole nitrogen presents the possibility of deprotonation under Birch-type conditions, and the resulting anion would be resistant to reduction. Initial studies began on the N-BOC pyrrole amide and ester **2/3** (**Scheme 1**) which were readily prepared in two steps from commercially available 2-(trichloroacetyl)pyrrole (**1**). Compounds **2** and **3** were designed to overcome both of the barriers to reduction that are outlined above. The carbonyl group was specifically chosen not only as an electron-withdrawing group, but also as a 'handle' by which we could introduce substituents at C-2 by reductive alkylation. We were delighted to find that a versatile and high yielding protocol for *reductive alkylation* could be achieved by employing sodium metal (**Scheme 1**).[1] The results presented show that the enolate species which is quenched in the final step of the reaction is very reactive towards a series of primary alkyl halides. 3,4-Dehydroproline derivatives were obtained by quenching the reaction with ammonium chloride.



Scheme 1

We propose that under the conditions outlined above, compounds **2** and **3** are able to accept two electrons and form a dianion: this would be protonated by ammonia at C-5, leaving an anion (enolate) at C-2 which can be quenched by addition of an electrophile.

Both the amide/ester and BOC protecting groups should be removable if this chemistry is to become synthetically useful. Treatment of **4** with HCl (aq.) at reflux secured removal of both the BOC and amide groups to yield the corresponding amino acid, which was conveniently purified as its N-acetyl derivative (**Scheme 2**). This transformation occurred without any detectable migration of the double bond at C-3. The advantage of carrying an ester through this sequence was realised when **5** was saponified to yield the acid in 75% yield (**Scheme 2**).[1] This methodology provides a practicable alternative to the amide substituted pyrrole reductions, and means that the carboxylic acid at C-2 may be liberated without deprotection of the amine.



Scheme 2

Extension of this methodology to explore the scope of this chemistry and to encompass the formation of enantiopure products is currently underway.

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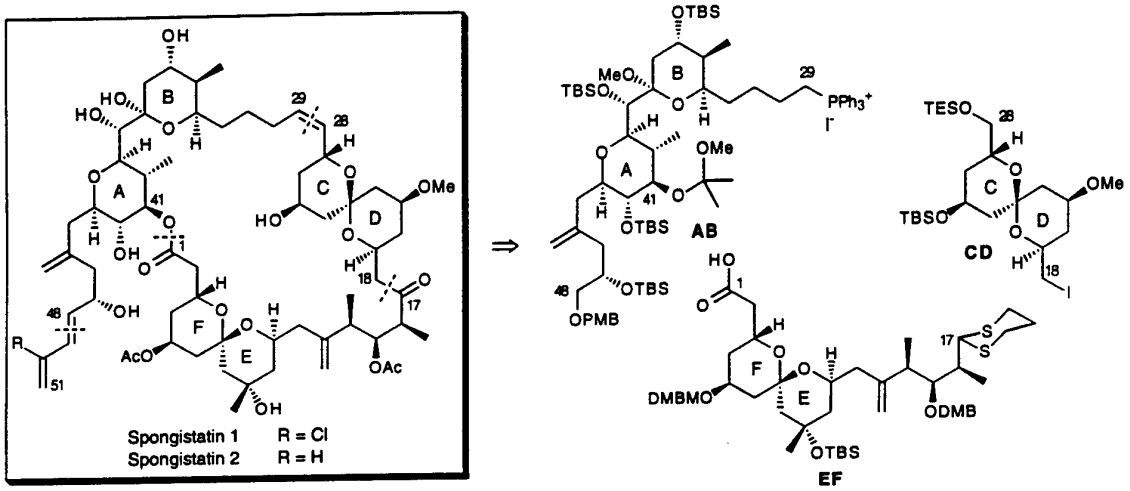
THE SPONGISTATIN (a.k.a. ALTOHYRTIN) ANTITUMOR AGENTS: ARCHITECTURALLY COMPLEX SYNTHETIC TARGETS

Amos B. Smith, III

Department of Chemistry, Laboratory for Research on the Structure of Matter, and Monell Chemical Senses Center, University of Pennsylvania, Philadelphia, PA 19104 U.S.A.

The spongistatins comprise a family of novel microtubule-assembly inhibitory agents, first isolated in 1982 by Pettit and co-workers[1] from an Indian Ocean sponge. Due however to the paucity of available material (average isolation yield 3.9 x 10^{-7}%), their relative and absolute stereochemistries remained undefined until 1993. In that year the Pettit[2] and Kitagawa[3] groups respectively reported the relative and absolute stereochemistries of spongistatin 1 (a.k.a. altohyrtin A). Spongistatin 1, the most abundant congener, proved to be "extremely potent (GI_{50}'s typically 2.5-3.5 x 10^{-11} M) against a subset of highly chemoresistant tumor types comprising the NCI panel of 60 human cancer cell lines." Moreover, "cell lines derived from human melanoma, lung, colon, and brain cancers were found to be especially sensitive to spongistatin 1."[2]



Given the architectural complexity of the spongistatins, in conjunction with their impressive antitumor activities and lack of availability, we inititated in 1994 a research program directed at their total synthesis. From the retrosynthetic perspective, disconnection of **1** and **2** into three fragments of essentially equal structural complexity leads to **AB**, **CD**, and **EF**. This analysis was envisioned to provide considerable flexibility, since fragment coupling could proceed in either a clockwise and counterclockwise fashion. Of equal importance, no new stereogenetic centers would be created.

Central to this synthetic venture has been the development of an efficient, "one-pot" multicomponent linchpin coupling of 2-lithio-2-trialkylsilyl-1,3-dithianes with a variety of electrophiles via controlled Brook rearrangement. The latter holds the promise of exceptionally concise routes to a wide variety of complex 1,3-polyol natural products, including the polyene macrocycles and macrolides.

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RECENT DEVELOPMENTS IN COMPUTER AIDED DESIGN OF EFFECT CHEMICALS

A Peter Johnson, School of Chemistry, University of Leeds.

There is considerable interest in the tailoring of an organic molecule to perform a specific function, such as the catalysis of a particular reaction, behaviour as a synthetic receptor for a particular small molecule, or the inhibition of a particular biological process by binding strongly to one of the macromolecule participants in such a way as to block the normal operation of the process. Great strides have been made in the manual design of such species, but the automation of elements of the design process might permit the critical evaluation of much larger numbers of potential 'effect chemicals'.

For the past several years our group in Leeds has been working on the development of a software suite designed to solve some of the problems associated with this automated design process. Although the resulting SPROUT system is designed to be be a general purpose aid to the solution of the problems outlined above, up to now the focus has concentrated on functionality which could aid the design of inhibitors of biological processes.

SPROUT provides a set of tools designed to aid the synthesis of *synthetically accessible* ligands which either fit a pharmacophore hypothesis or are predicted to bind strongly to a particular 3-D structure of a protein. The CANGAROO module identifies clefts in a protein which might serve to bind ligands and the HIPPO module characterizes the receptor site of a protein and identifies potential "hot spots" or *target sites* where suitable ligand atoms might be positioned for binding to the protein by H-bonding, covalent interactions, metal ligand interactions and hydrophobic interactions.

Other modules dock small fragments to these sites and connect them together by an exhaustive growing process akin to the construction of Dreiding models is evaluated in the course of a few hours). For some problems, this process can generate thousands of structures which fit the design constraints and the ALLIGATOR module provides clustering and ranking tools which permit the user to navigate through the as an empirical scoring function which attempts to estimate binding affinity. In the final step, the CAESA module is used to provide an estimate of the ease of synthesis of each of the suggested molecules. It achieves this through a more sophisticated estimate of molecular complexity which is combined with a retrosynthetic analysis to find suitable readily available starting materials.

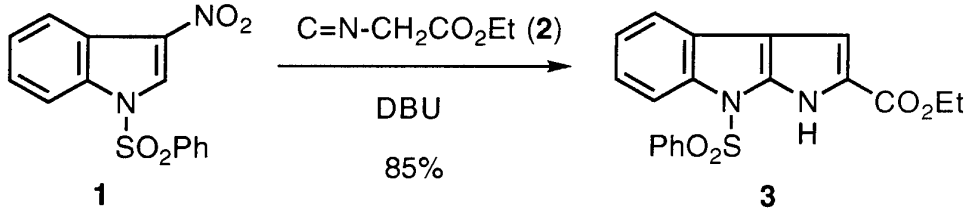
Examples of the application of SPROUT to inhitor design will be presented.

NOVEL INDOLE CHEMISTRY IN THE SYNTHESIS OF NATURAL PRODUCTS

Gordon W. Gribble

Department of Chemistry, Dartmouth College, Hanover, NH 03755, USA

Indole and the myriad natural products that contain the indole ring system have played a central role in the development and exploration of heterocyclic chemistry and natural products chemistry for 100 years. Despite this long pivotal and historical role in organic chemistry, new indole chemistry continues to be discovered. This lecture will present some of the work in the author's laboratory involving metalation and cycloaddition chemistry of indoles leading to the synthesis of indole-containing natural products. For example, we have recently discovered a one-step synthesis of the 1,8-dihydropyrrolo[2,3-*b*]indole ring system **3**, which is embodied in the pyrroindomycin antibiotics. Thus, a Barton-Zard reaction of 3-nitroindole **1** with ethyl isocyanoacetate (**2**) and DBU gives **3**, rather than the expected 2,4-dihydropyrrolo[3,4-*b*]indole ring system.



1 **3**

ABSTRACTS

POSTER PRESENTATIONS

13TH LAKELAND HETEROCYCLIC SYMPOSIUM
GRASMERE 8 - 12 MAY 1997

SOME APPLICATIONS OF PALLADIUM AND COBALT TO HETEROCYCLE SYNTHESIS

Roderick W. Bates, Thota Rama-Devi and Jianhua Ji
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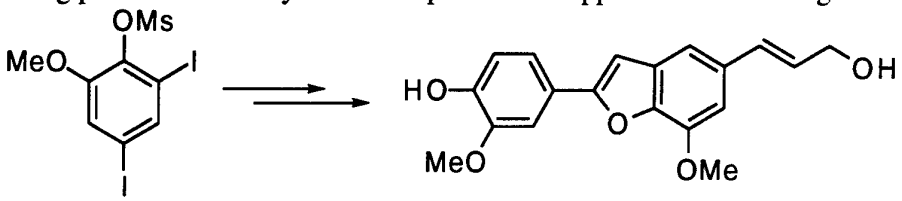
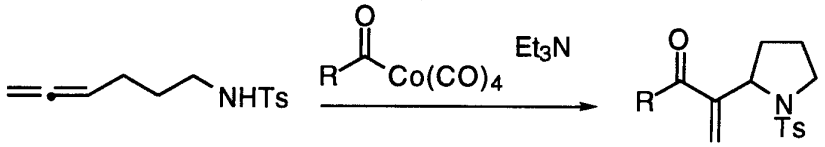
The role of organotransition metal reagents in Organic Synthesis is now unassailable. Two of our projects in this area led, not quite intentionally, into the area of heterocyclic synthesis.

In the last step of a synthesis of a fungal phytotoxin, the facile nature of the conversion of *ortho*-alkynylphenols to benzofurans became painfully apparent to us.[1] This was subsequently employed in a short synthesis of Ailanthoidol, a recently isolated natural benzofuran.[2] The three key C-C bond forming processes in the synthesis are palladium-copper mediated Sonogashira reactions.

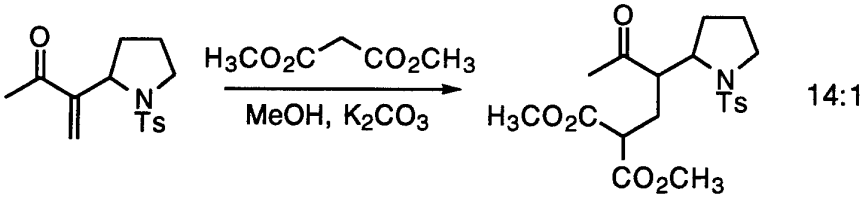


A less frequently used metal is cobalt. It has been known for years that 1,2- and 1,3-dienes are converted to electrophilic π-allyl complexes on reaction with acyl cobalt reagents. We have performed this reaction in an intramolecular sense to generate tetrahydrofurans and pyrrolidines.[3] The sulfonamide group is particularly useful as a nucleophile.



The reaction can be applied to mono- and di-substituted allenes. With internal disubstituted allenes, a single geometrical isomer of the product is obtained, provided that work-up is prompt!

The products are good Michael acceptors and, with dimethyl malonate, the product is formed with high diastereoselectivity.



In non-protic solvents, the reaction takes a different course and addition-elimination occurs

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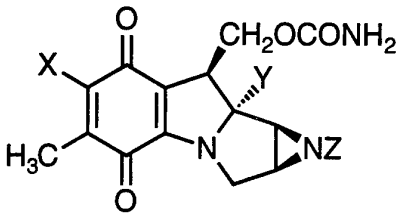
A RADICAL APPROACH TO THE SYNTHESIS OF MITOMYCIN

Shirley Brunton and Keith Jones.
King's College London, Department of Chemistry, Strand, London WC2R 2LS.

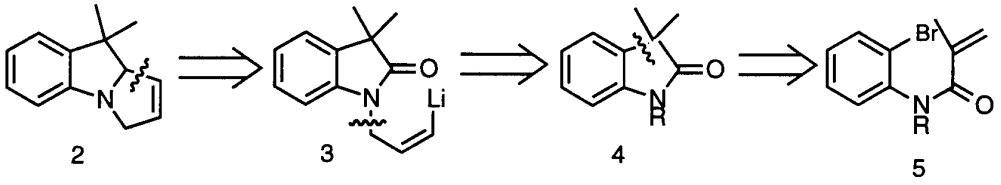
The mitomycins are a group of antibiotics all containing the common structure **1**.



mitomycin C X=NH_2 Y=OMe Z=H

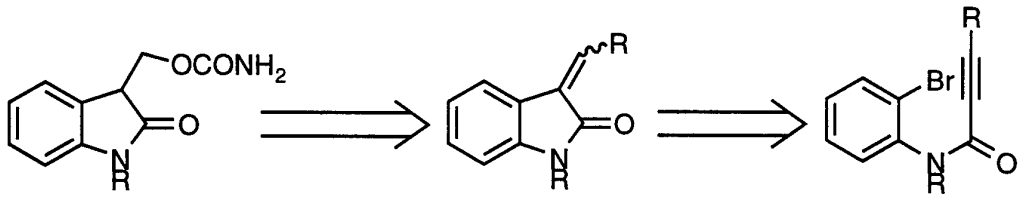
1

Disconnection of the mitomycin skeleton **2** takes the molecule back to an N-alkylated oxindole **3**, which can be further disconnected back to the simple oxindole **4**. This has been prepared via a 5-exo aryl radical cyclisation of the amide **5** [1,2].



2 3 4 5

We have also performed 5-exo-dig aryl radical cyclisations on amides such as **8**. This generates the the oxindole**7**, which contains an exocyclic double bond. This may provide a useful handle with which to introduce the desired carbamate group.



6 7 8

Aryl radical additions on to carbon triple bonds are relatively rare. Our work in this area will be presented.

References

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2. C. M^{c}Carthy and K. Jones, *J Chem. Soc, Chem. Commun.*, 1989, 1717.

13TH LAKELAND HETEROCYCLIC SYMPOSIUM
GRASMERE, 8-12 MAY 1997

NOVEL CALIX[4]RESORCINARENE GLYCOSIDES

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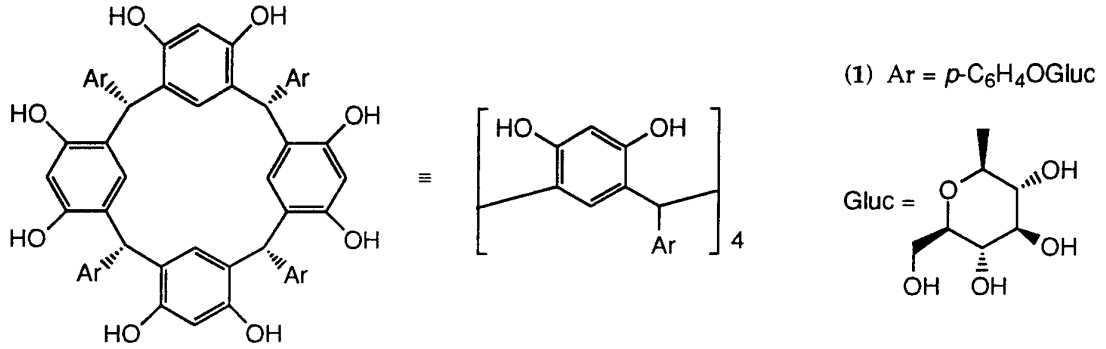
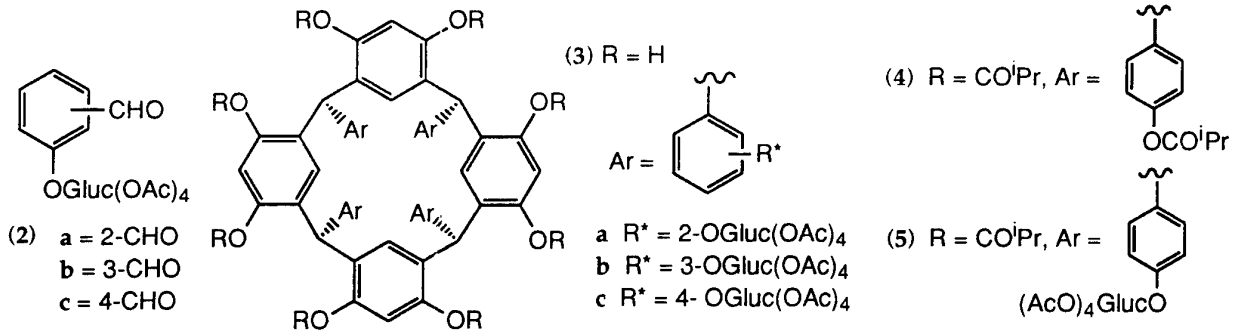
Calix[4]resorcinarenes have been used profitably by several workers, notably Cram, Reinhoudt and Aoyama.[1] They may be prepared from the reaction of a resorcinarene and an aldehyde in ethanolic hydrochloric acid, conditions which obviously do not tolerate acid-sensitive starting materials. A recent report briefly described their synthesis using Lewis acid catalysis.[2] We have developed this method into an efficient route to resorcinarene glycosides, such as compound (**1**), compounds which are inaccessible by any other route.



Thus, aldehydes (**2a-c**) were reacted with resorcinol in the presence of aluminium chloride to deliver resorcinarenes (**3a-c**), the ratio of conformational isomers of each compound being determined by ^{1}H NMR analysis of the octabutyrates. The structure of compound (**3a**) was proved *via* a sequence of reactions which yielded known compound (**4**); this also gave an estimate of the ratio of conformers of the butyrate (**5**) and, hence, resorcinarene (**3a**).



Resorcinarenes which bear a glycosyl moiety on either the upper- or lower-rim have been prepared and may find use as chirally-modified receptors, catalysts or carcerands.

References:

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A CYCLOADDITION ROUTE TO HETEROCYCLIC TRIONES

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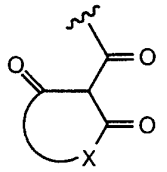
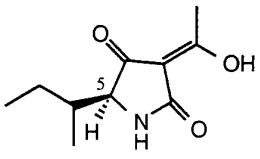
Introduction

The heterocyclic trione system **1** is a constituent of several classes of biologically active natural products. We present new synthetic methodology towards the 3-acyltetramic acids such as tenuazonic acid **2**, which shows antibacterial and anti-viral activity, and the pyridone ilicicolin H.



1 X = O, NR



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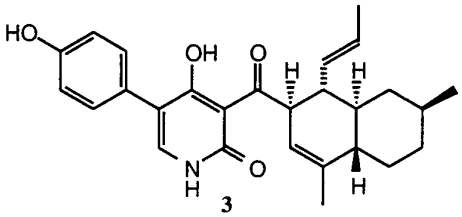


3

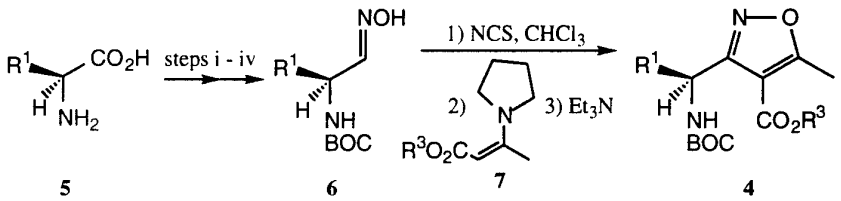
Discussion

The key step of our strategy is to mask the highly polar, enolic trione system as a 4-carboxyisoxazole **4** to alleviate problems of separation and purification and allow for the generation of the trione late in the synthesis. Using α-amino acids **5**, to introduce R^1 stereospecifically, we have synthesised oximes **6**. Conversion of **6** into the nitrile oxides was followed by a 1,3-dipolar cycloaddition with enamine **7** which resulted, after elimination of pyrrolidine, in formation of the 4-carboxyisoxazoles **4**.

Reagents i, CH_3COCl, MeOH;
ii, $O[CO_2C(CH_3)_3]_2$, Et_3N, CH_2Cl_2;
iii, DIBAL-H, Toluene, -78°C;
iv, $NH_2OH.HCl$, NaOAc, EtOH aq.

BOC = *tert*-butyloxycarbonyl

R^1 = Me, ^{n}Bu, ^{i}Bu; R^3 = Et, ^{t}Bu

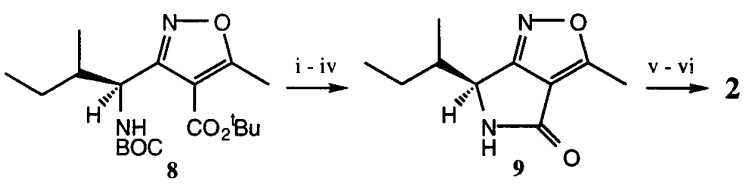


5 **6** **7** **4**

Deprotection of the amino and carboxy groups of ester **8** was followed by a carbodiimide – mediated cyclisation to the lactam **9**. The N–O bond of the isoxazole was cleaved by hydrogenolysis and on hydrolysis the natural product tenuazonic acid **2** was isolated as a 4:1 epimer mix at C–5 with the natural product as the major component.

Reagents i, TFA, 25°C; ii, 2M HCl aq., 25°C;
iii, HOSu, EDCI, DMF, 0°C; iv, Et_3N, 25°C;
v, H_2, 1 atm, Pd-C, MeOH, 25°C;
vi, 2 M NaOH aq., 25°C.

BOC = *tert*-butyloxycarbonyl



8 **9** **2**

Conclusion

The synthesis of tenuazonic acid has proved the viability of our novel strategy. The extension of this strategy to enantiomerically pure material and the pyridone metabolites will also be described.

13TH LAKELAND HETEROCYCLIC SYMPOSIUM
GRASMERE, 8-12 MAY 1997

AN UNEXPECTED PRODUCT FROM THE REACTION OF 2-CHLORO-3-NITRO THIOPHENE WITH 2-BENZYLIMIDAZOLINE†

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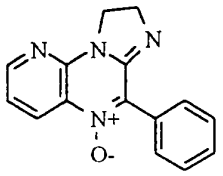
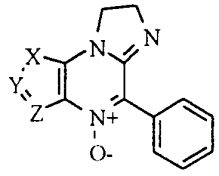
Derivatives of the heterocyclic mono-*N*-oxides (**1**) are of potential interest as bioreductive anti-tumour drugs.[1] As part of an exploration of the relationship between anti-tumour activity and chemical structure we have investigated the synthesis and properties of some five-membered analogues with general structure (**2**). Imidazole and pyrazole analogues were prepared by reaction of the corresponding 4-nitro-5-halo heterocycles with 2-benzylimidazoline followed by base catalysed cyclisation.[2] .

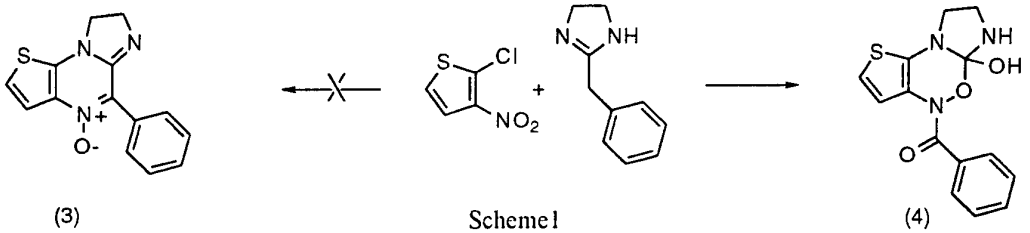


(1)



(2) X,Y,Z = N, NR or CR

When the corresponding reaction with 2-benzylimidazoline was carried out using 2-chloro-3-nitrothiophene none of the desired *N*-oxide (**3**) was formed (Scheme1). Instead, at room temperature a cyclisation product slowly forms to which we have tentatively assigned the structure (**4**). Product (**4**) does not form in the absence of oxygen. Under anaerobic conditions a reactive intermediate can be detected and exposure to oxygen rapidly leads to the formation of product (**4**). The details of this transformation and possible mechanisms will be discussed.



(3) Scheme1 (4)

References

1) M. A. Naylor, M. A .Stephens, J . Nolan, B . Sutton, J. H. Tocher, E. M. Fielden, G. E. Adams & I. J. Stratford, *Anti-cancer Drug Design*, 1993, **8**, 439-461.

2) Elba Bujan de Vargas, A. Irene Canas, *Tetrahedron Letters*, 1996, **36** (6), 767-770.

† This work was supported by the Cancer Research Campaign

A DECONJUGATION - ALKYLATION ROUTE TO NOVEL ANALGESICS

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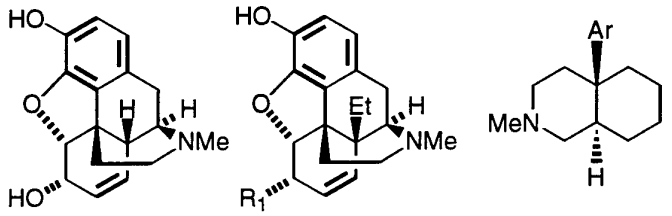
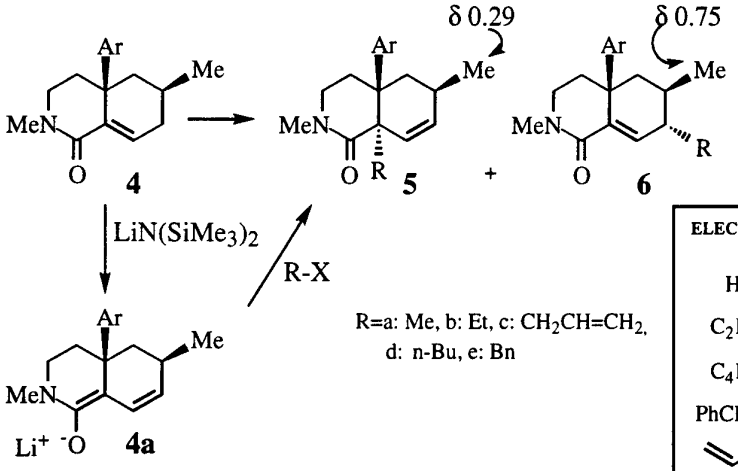
King's College London, Strand, London, WC2R 2LS

The management and alleviation of acute and chronic pain remains one of the most difficult and vexing problems in medicine. Arguably morphine **1** and its numerous synthetic analogues remain the most important and widely used analgesics for the treatment of such pain. Unfortunately, the severe side-effects of morphine and the vast majority of it's analogues, in particular their dependence capacity frequently limit their use. The separation of analgesia and dependence has been the goal of researchers for many years.

One hopeful solution to this problem may lie in the observation that substitution at C-14 of the morphine skeleton (e.g. to give **2**) greatly increases the analgesic properties but decreases the severity of the unwanted side effects. However, the synthesis of these compounds is not trivial and so access to these structures has been difficult. The simple *trans* -decahydroisoquinoline analogues **3** also show good analgesic activity. Thus it would be interesting to see the effect of ring junction substitution on the analgesic activity of these structures. Here we report the synthesis of ring junction substituted octhydroisoquinolones **5** by deconjugation - alkylation of the parent isoquinolone **4**. A second product, the γ -alkylated product **6** was also formed as the minor constituent.

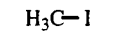


1 **2** **3**

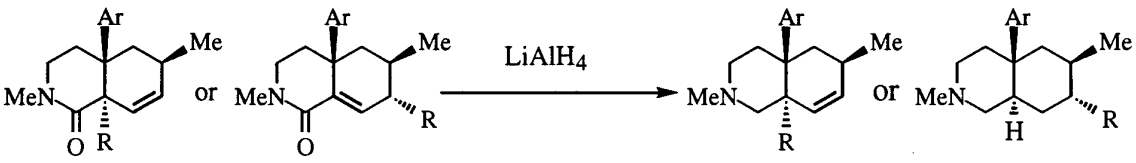


R=a: Me, b: Et, c: $CH_2CH{=}CH_2$, d: n-Bu, e: Bn

The relative stereochemistry of the new chiral centres was determined by nmr

ELECTROPHILE	TOTAL YIELD α + γ	REGIOSELECTIVITY α / γ
H_3C-I	58%	91/9
C_2H_5-I	54%	60/40
C_4H_9-I	60%	51/49
$PhCH_2-I$	60 %	67/33
	50%	63/38

Reduction of these should then lead to the biologically active molecules **7** and **8.**



5 **6** **7** **8**

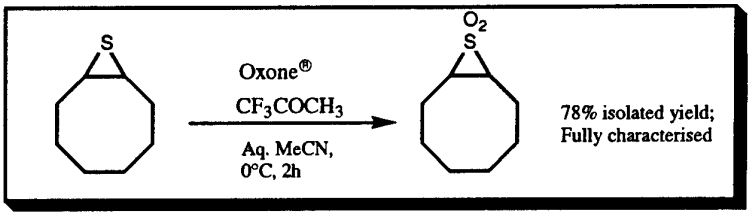
13TH LAKELAND HETEROCYCLIC SYMPOSIUM
GRASMERE, 8-12 MAY 1997

THE FIRST PREPARATION OF EPISULFONES FROM EPISULFIDES: OXIDATION USING OXONE®/TRIFLUOROACETONE

Paul Johnson and Richard J. K. Taylor
Department of Chemistry, University of York, York YO1 5DD

A wide range of organic sulfides, both acyclic and cyclic, are easily oxidised to give the corresponding sulfoxides and sulfones. Episulfides (thiiranes), however, have proved anomalous: under controlled conditions they can be oxidised to episulfoxides but there are no authenticated reports of episulfones being prepared from either episulfides or episulfoxides by an oxidative pathway.[1] This is not through lack of effort: a range of oxidants including nitric acid, potassium permanganate, hydrogen peroxide, perbenzoic acid, metachloro-perbenzoic acid, benzoyl peroxide, sodium periodate, ozone, sodium peroxide in methanesulfonic acid, pertrifluoromethanesulfonic acid, and singlet oxygen have been employed without success.[1] We have shown that episulfones can be prepared from α–halosulfones under modified Ramberg-Bäcklund conditions[2] but, for our investigations into synthetic applications of episulfones,[3] we required easy access to a range of simple episulfones. We therefore decided to reinvestigate the episulfide oxidation route.

We now report that certain episulfides are efficiently oxidised to episulfones using Oxone®/trifluoroacetone:[4]



The scope and limitations of this procedure will be discussed, as will mechanistic implications. We will also report an improved procedure for the oxidation of episulfides to episulfoxides.

1. For a review of attempts to prepare episulfones by episulfide oxidation see U. Zoller, Chapter 9 in The Chemistry of Sulphones and Sulphoxides, Eds. S. Patai, Z. Rappoport, C. J. M. Stirling, John Wiley, Chichester, 1988 (pp. 413-419).
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4. D. Yang, M. K. Wong, Y. C. Yip, *J. Org. Chem.*, 1995, *60*, 3887.

HETEROCYLIC ENEDIYNES AS PROBES OF BIOMOLECULE FUNCTION

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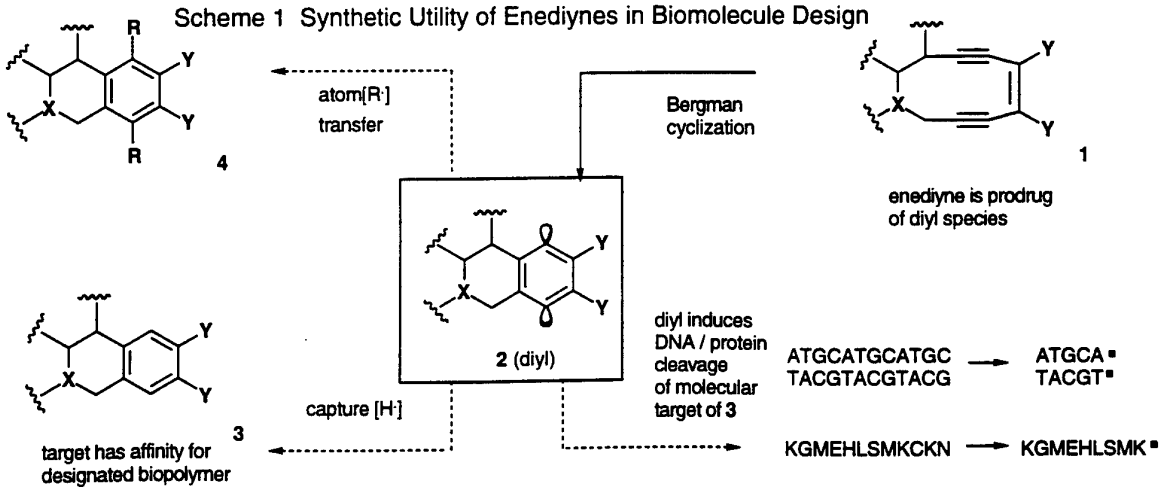
Department of Chemistry, Clemson University, Clemson, SC, 29634-1905, USA

Interest in the chemistry of enediynes has grown steadily over the past decade, fuelled both by reports of their antitumor activity, and their intriguing and challenging molecular structures.[1] In additon to inflicting lesions in DNA, which in turn may activate suicide repair pathways, [2] a number of enediynes have been reported to induce protein degradation and agglomeration.[3] The goal of our investigation is to highlight synergy between the biological and synthetic utility of enediynes, by focusing on the intermediates of enediyne cyclization - diyl radicals. As depicted in Scheme 1, by selecting specific targets **3**, which incorporate a minimum effective subunit required for a particular biological response, their subsequent synthesis from diyls **2** can be envisioned, *via* controlled cycloaromatization of enediynes **1**. Moreover, if the biological targets of **3** are defined, the effects of **2** on these targets can then be assessed, providing insight both to receptor topology and to small molecule-receptor interactions. Examples of such interactions include receptor and enzyme proteolysis events, and nucleotide / nucleoside fragmentation. For synthetic purposes, specific atom transfer reactions with diyl **2** could also be performed, to yield analogs of target **3** i.e. **4**. The pursuit of these studies has already resulted in new developments in enediyne chemistry, and in the identification of new affinity cleavage systems.

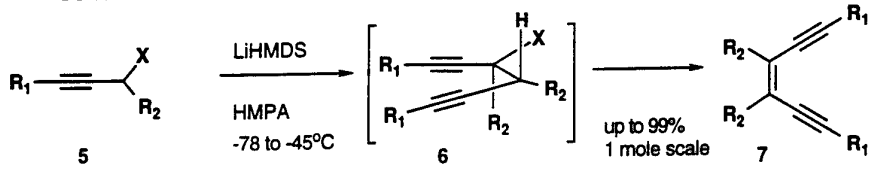
Scheme 1 Synthetic Utility of Enediynes in Biomolecule Design



In order to execute the above studies, new methods for the synthesis of enediynes were developed in this laboratory. It was found that propargylic halides **5** (X=Hal), when converted to the corresponding lithio

halocarbenoid species, undergo coupling reactions to produce haloalkynes **6** (Scheme 2).[4] Under mild conditions, these species undergo *in situ* elimination to give enediynes **7** directly.

Scheme 2. Carbenoid insertion-elimination route to enediynes



A variety of substituted linear enediynes are available using this process,[5] and, *via* the intramolecular variant, both carbocyclic and heterocyclic systems.[6] In the latter case, this method offers a high yielding alternative to the traditional Ramberg-Backlund approach. Additionally, since ring formation takes place at low temperature, competing Bergman cyclization of the product enediynes is avoided. We have incorporated this chemistry in the preparation of bifunctional agents directed at nucleic acids,[7-8] the human estrogen receptor (hER),[9] and the aryl hydrocarbon receptor (AhR).[10] Recent developments in these areas will be highlighted, together with other ongoing applications.

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A RADICAL ROUTE TO THE MONOTERPENE ALKALOIDS OXERINE AND ACTINIDINE

Andrea Fiumana, Keith Jones and Maria Luisa Escudero Hernandez
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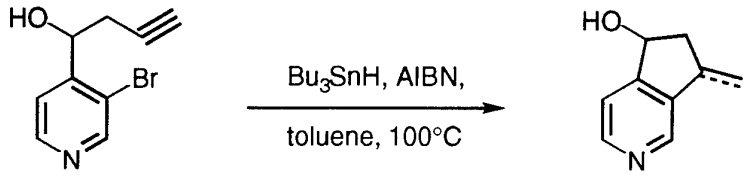
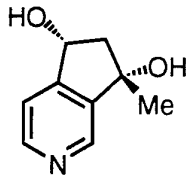
We have developed the use of aryl radicals in the synthesis of a range of heterocyclic systems including some oxindole-based natural products. However, the generation and use of heteroaryl radicals has received far less attention. In addition to some indole-radical cyclisations, we have recently been investigating the generation and cyclisation of pyridine radicals in synthesis.

Pyridine radicals, generated from 3-bromopyridines using the tributyltin hydride method undergo both cyclisation onto suitably positioned alkenyl and alkynyl acceptors (scheme 1) as well as the expected intramolecular hydrogen atom abstraction process.



Scheme 1

We have used this chemistry as the basis for short and efficient syntheses of the two monoterpene-derived alkaloids (±)-oxerine **1** and (±)-actinidine **2** which contain the cyclopentanopyridine skeleton.



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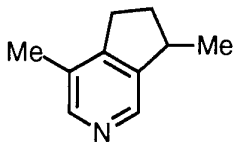

2

References

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13TH LAKELAND HETEROCYCLIC SYMPOSIUM
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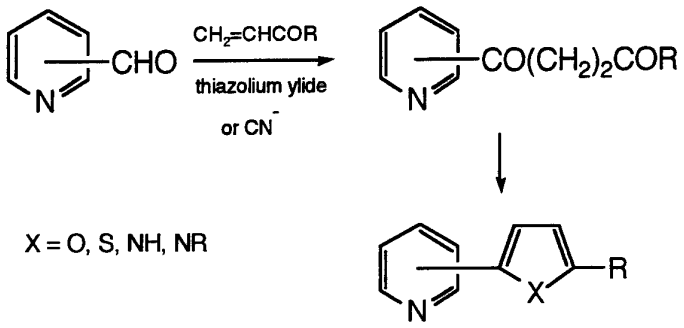
ALTERNATING π-ELECTRON DEFICIENT:π-EXCESSIVE HETEROAROMATIC OLIGOMERS AND POLYMERS.

R.A. Jones, M. Karatza, T.N. Voro, P.U. Civcir, A. Franck, O. Ozturk, J.P. Seaman, A.P. Whitmore and (the late) D.J. Williamson.

School of Chemical Sciences, University of East Anglia, Norwich, NR4 7TJ, UK

As part of our programme to produce extended alternating π-electron deficient:π-electron excessive heteroaromatic systems, which may have semi-conducting and/or non-linear optical properties, we have prepared compounds of the type **1** - **4** from formyl and acetylpyridines using a combination the Stetter and the Paal-Knorr reactions,[1,2] an example of which is shown in the following reaction sequence.



1 R = Me or Ph; **2** R = 2, 3 or 4-pyridyl

3 R = Me, Ph, 2-pyridyl **4**

The compounds are best characterised by their ^{13}C NMR spectra, the spectra for the polymers **4** being obtained in the solid state. Molecular modelling suggests that the preferred conformation of **4** is helical. Kinetic studies[3] show that relative reactivities toward quaternisation of the isomers are 4-pyridyl > 3-pyridyl >> 2-pyridyl and that the order of activity for the 2-pyridyl systems **1** is O ~ S >NR >> NH. This can be interpreted in terms of steric and, for X = NH, H-bonding shielding of the pyridine N atom. Similarly, quaternisation of 3-(2-pyrrolyl)pyridazine occurs on N^1 and not N^2 of the pyridazine ring.[4,5]

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13TH LAKELAND HETEROCYCLIC SYMPOSIUM
GRASMERE, 8 - 12 MAY 1997

PYRROLOINDOLE ANALOGUES OF ELLIPTICINE. THE SYNTHESIS AND DNA INTERCALATIVE PROPERTIES OF 5,10-DIHYDRO-5,10-DIMETHYL-2,5,10-TRIAZABENZO[a,e]PENTALENE

R.A. Jones,[a] J. Bakboord,[a] J. Pastor,[b] J. Siro[b] and T.N. Voro.[a]

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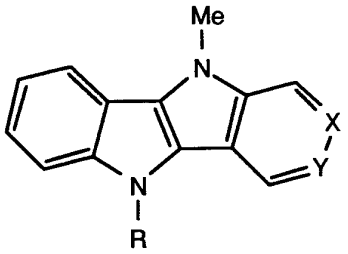
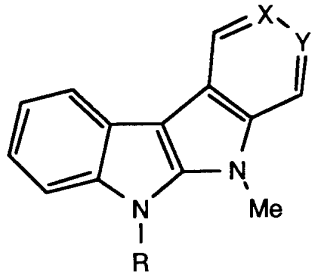
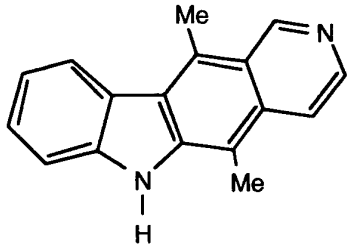


1a R = H or Me, X = N, Y = CH
1b R = H or Me, X = CH, Y = N

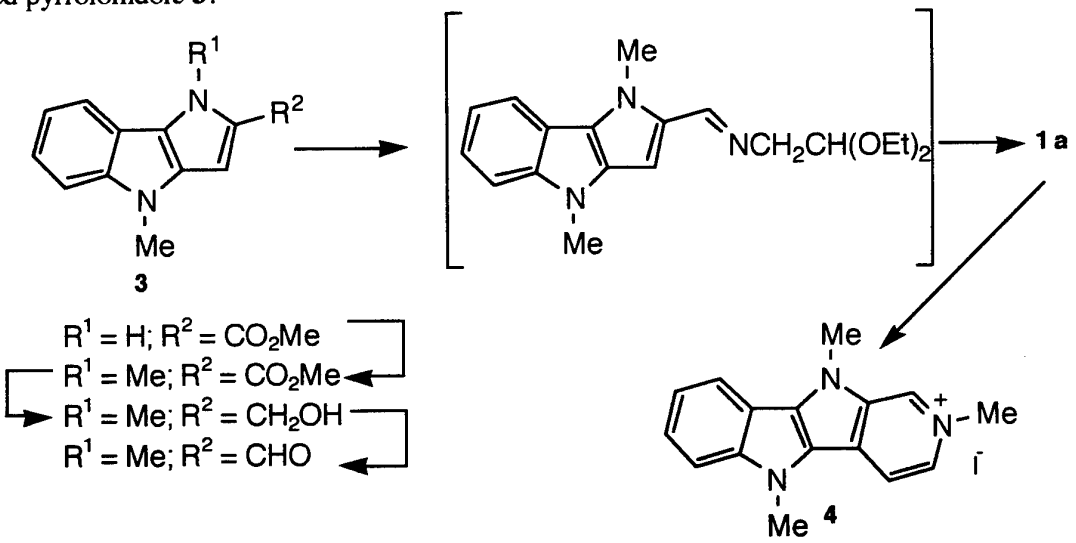


1c R = H or Me, X = N, Y = CH
1d R = H or Me, X = CH, Y = N



2

As part of a programme to prepare and evaluate the biologicxal activity of pyrroloindole analogues of ellipticine **2**, we have embarked on the synthesis of compounds **1a** - **1d**. Compound **1a** (R = Me) and its methiodide **4** have been prepared[1] according to the following reaction sequence starting from the previously described pyrroloindole **3**.[2]



Examination of the intercalation properties of **1a** into DNA show it to have an association constant and site binding properties which are closely comparable with those for ellipticine

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13TH LAKELAND HETEROCYCLIC SYMPOSIUM

GRASMERE, 8-12 MAY 1997

TROST'S LIGANDS FOR PALLADIUM(0) CATALYZED ASYMMETRIC ALLYLIC SUBSTITUTIONS

Ian C. Lennon

Chiroscience Ltd. Cambridge Science Park, Milton Road, Cambridge, CB4 4WE, UK.

Professor Barry M. Trost has recently introduced a family of chiral ligands[1-3] that have proven to be extremely versatile in palladium(0) catalyzed asymmetric substitutions for the synthesis of chiral heterocyclic products such as carbovir,[3] aristeromycin,[3] (+)-pancratistatin,[4] *N*-phthalimido-protected vinyl glycinol[5] and *N*-phthalimido-protected vigabatrin.[6]

Chiroscience in collaboration with Professor Trost and Stanford University have developed this methodology into a useful technology for asymmetric synthesis. The ligands can now be produced on a commercial scale by a concise and efficient procedure developed at Chiroscience.

This poster details the range of chiral ligands available, the types of nucleophile successfully employed, and the plethora of substrates that have been utilised. In most cases excellent levels of optical purity are observed, typically 90 - 99% ee, and the reactions generally give chemical yields greater than 85%. Optimisation of the reaction conditions, that allow as little as 0.05 mol% palladium and 0.06 mol% ligand to be used, is also discussed.

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6. Trost, B. M.; Lemoine, R. C. *Tetrahedron Letters* **1996**, *51*, 9161.

APPROACHES TO OPTICALLY ACTIVE N-(2-AMINOETHYL)HYDROXYLAMINES AS PRECURSORS FOR HETEROCYCLIC HOMOCHIRAL NITRONES

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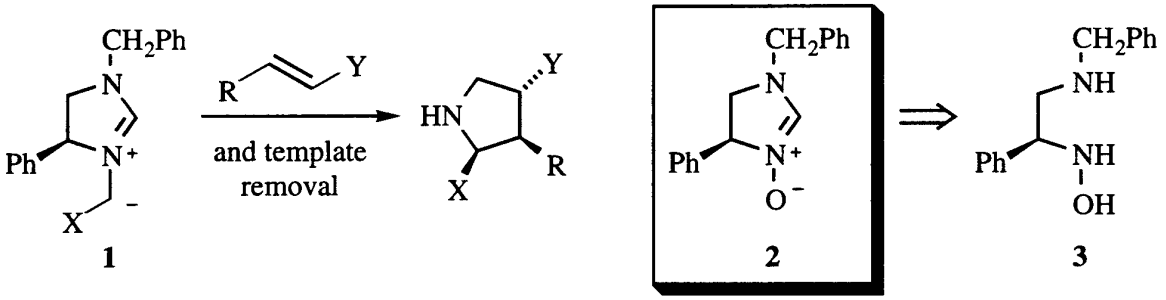
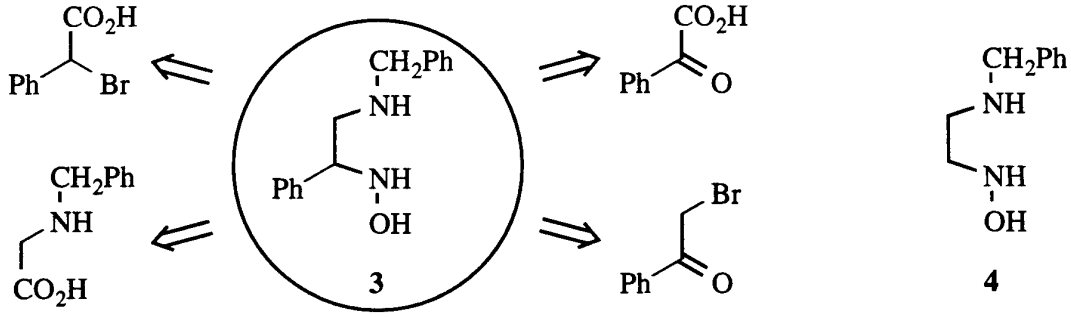
Chemistry Department, The Open University, Walton Hall, Milton Keynes MK7 6AA, UK

As part of an ongoing programme to develop optically active reagents for heterocycloaddition reactions, we have previously prepared the azomethine ylide **1** and its enantiomer, based on the imidazoline moiety. 1,3-Dipolar cycloaddition of these facially differentiated reagents afforded a route to optically active pyrrolidines.[1] We wish to extend this approach to generate the related homochiral nitrone **2** and its enantiomer. Utilization of the isoxazolidines formed from cycloaddition of nitrones is an established tactic in synthesis; N–O bond cleavage and recyclization to saturated heterocycles is one example.



Our synthetic strategy for assembly of **2** requires the optically active N-(2-aminoethyl)hydroxylamines **3** as building blocks, and we will present our studies towards the synthesis of **3** and its achiral counterpart **4**. Progress in approaches to **3** from 2-bromophenylacetic acid, from benzoylformic acid, from 2-bromo-acetophenone, and from N-benzylglycine will be outlined.[2]



1. Jones, R. C. F.; Howard, K. J.; Snaith, J. S. *Tetrahedron Lett.*, **1996**, *37*, 1707-1710; 1711-1714; *Tetrahedron Lett.*, **1997**, *38*, 1647-1650.

2. We thank EPSRC, SB Pharmaceuticals and Dr Paul S Smith for helpful discussions and financial support..

13TH LAKELAND HETEROCYCLIC SYMPOSIUM
GRASMERE, 8-12 MAY 1997

A MILD ROUTE TO HETEROCYCLIC ACETIC ACIDS USING SODIUM PERBORATE TETRAHYDRATE

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[b]Knoll Pharmaceuticals, Pennyfoot Street, Nottingham, NG1 1GF, U.K.

As part of a synthetic project we wished to synthesise the imidazole acetic acid derivatives (**3**) by decarbonylation of the pyruvic acids (**2**) that are readily prepared by functionalisation of the acidic 2-methyl substituents of the 5-nitroimidazoles (**1**). Standard methods of decarbonylation did not work, presumably due to intramolecular hydrogen bonding in the pyruvate precursor. We have found that aqueous sodium perborate tetrahydrate provides a convenient , mild and high yielding method for achieving the transformation **2** to **3**,[1] and we have now demonstrated that this methodology is applicable to a variety of aromatic and heteroaromatic pyruvic acid derivatives.

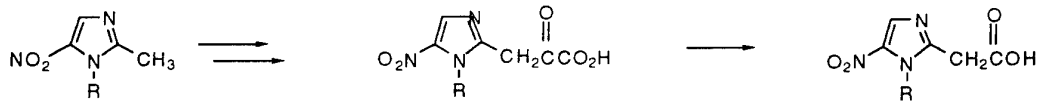

Table Oxidation of Aromatic Pyruvic Acids using Sodium Perborate Tetrahydrate
[Ar-$CH_2CO.CO_2H$ → Ar-CH_2CO_2H]

Ar	Yield (%)
2-(1-Methyl-5-nitroimidazolyl	81
2-Thienyl	68
2-Pyridyl	86
3-Pyridyl	82
3-Indolyl	71
Phenyl	76
4-Hydroxyphenyl	80

References

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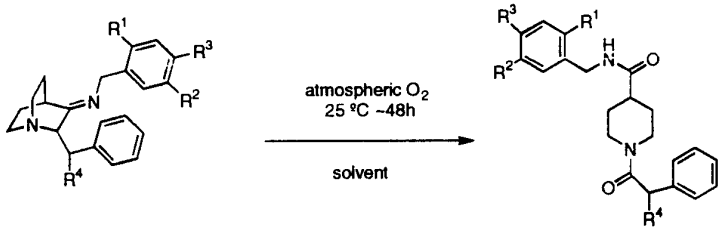
13TH LAKELAND HETEROCYCLIC SYMPOSIUM
GRASMERE, 8 - 12 MAY 1997

AN UNUSUAL OXIDATION REACTION WITH ATMOSPHERIC OXYGEN; FORMATION OF PIPERIDINES FROM 1-AZABICYCLO[2.2.2]OCTANES.

Timothy Norris* and Dinos Santafianos, *Pfizer Central Research Laboratories, Groton, CT 06340.*

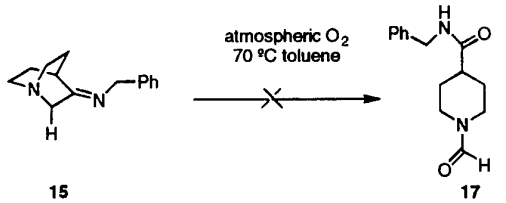
ABSTRACT: Examples where oxygen reacts directly with an imine causing scission between the α and β carbon atom have not been reported. If, however, tautomerism between the imine and corresponding enamine occurs in solution, the result of the reaction we observed with 2-benzhydryl-3-alkylimino-1-azabicyclo[2.2.2]octanes **1-7** and molecular oxygen does bear a superficial resemblence, in terms of outcome, to the reaction of triplet oxygen and an enamine in the presence of a copper catalyst,[1] or with singlet oxygen and an enamine.[2] The reaction we discovered is puzzling because the tendancy to tautomerize from the imine to the enamine is disfavored by the molecular architecture of the azabicyclo[2.2.2]octane ring system and the oxidation reaction occurs at room temperature without the aid of a catalyst. Speculation on the mechanistic pathway is therefore of interest.

Molecular oxygen reacts with 2-(1'-phenylethyl) and 2-benzhydryl-3-alkylimino-1-azabicyclo[2.2.2]octanes **1-7** in neutral solution at room temperature to form 1-acylpiperidine-4-carboxylic acid N-alkylamides **8-14**. During the transformation two new carbonyl bonds are formed and a carbon - carbon bond is cleaved. The transformation is quite general provided the 2-substituent of the imine is of sufficient steric bulk, such as 2-(1'-phenylethyl) or 2-benzhydryl. No reaction is observed in the absence of a 2-substituent as in the case of imine **15**.



1-7 **8-14**

1, 8: R^1,R^2, R^3 = H, R^4 = Ph; **2, 9**: R^1 = OMe, R^2 = *i*Pr, R^3 = H, R^4 = Ph; **3, 10**: R^1 = OMe, R^2, R^3 = H, R^4 = Ph; **4, 11**: R^1 = H, R^2 = Me, R^3 = H, R^4 = Ph; **5, 12**: R^1,R^2, R^3 = H, R^4 = Me; **6, 13**: R^1,R^2 = H, R^3 = OMe, R^4 = Ph; **7, 14**: R^1,R^2 = H, R^3 = Me, R^4 = Ph.



15 **17**

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CHIRAL BASE-MEDIATED DESYMMETRISATION OF SUBSTITUTED *meso*-CYCLOHEXENE OXIDES

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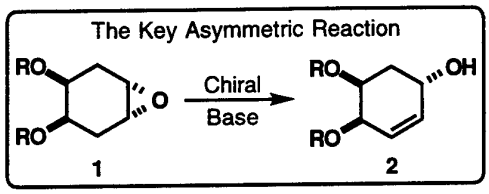
Department of Chemistry, University of York, Heslington, York YO1 5DD UK

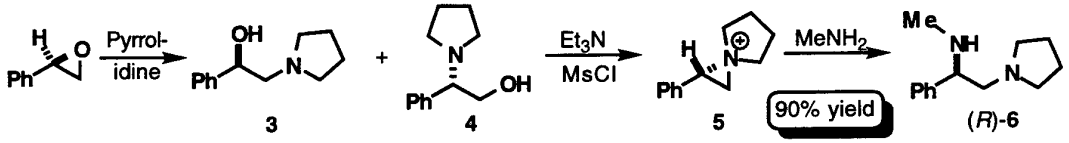
Epoxides can be transformed into optically active allylic alcohols using chiral versions of LDA.[1] Currently, our research is centred around the chiral base-mediated rearrangement of substituted *meso*-cyclohexene oxides **1** to allylic alcohols **2**. It is hoped that such desymmetrisation reactions will be useful tools in organic synthesis.



Two different aspects of our research will be presented in this poster:

1. A simple and efficient method for the preparation of homochiral amines

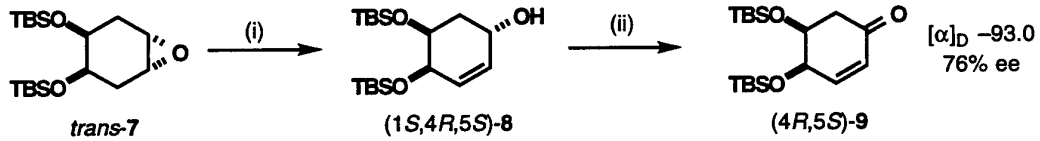
The full details of our recently reported[2] one-pot method for the preparation of homochiral amines (precursors to chiral bases) will be presented. For example, diamine (*R*)-**6** can be prepared in 90% yield starting from (*R*)-styrene oxide: mesylation of a 70:30 mixture of regioisomers **3** and **4** generates aziridiniun ion **5** which is opened regio- and stereospecifically at the benzylic position by methylamine.



Our new one-pot procedure is much shorter and more efficient (in terms of yield and convenience) than other synthetic approaches.

2. Chiral base-mediated rearrangement of substituted *meso*-cyclohexene oxides

Epoxide *trans*-**7** was prepared in four steps starting from 1,4-cyclohexadiene. Rearrangement of this epoxide with the chiral lithium amide base derived from diamine (*R*)-**6** generated allylic alcohol (1*S*,4*R*,5*S*)-**8** with 76% ee in 93% yield.[3] Subsequent oxidation afforded enantiomerically enriched enone (4*R*,5*S*)-**9**, a potentially useful chiral building block.



Reagents: (i) 1.3 eq (*R*)-**6**, 1.3 eq BuLi, THF, 0 °C → rt; (ii) 1.3 eq PDC, CH_2Cl_2, rt, 4 h

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THE NITRILE OXIDE / ISOXAZOLINE APPROACH TO 3-DEOXY-2-ULOSONIC ACID ANALOGUES

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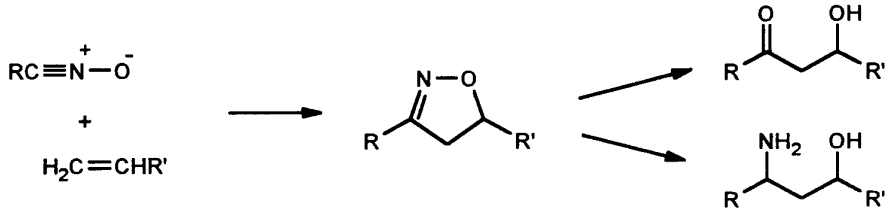
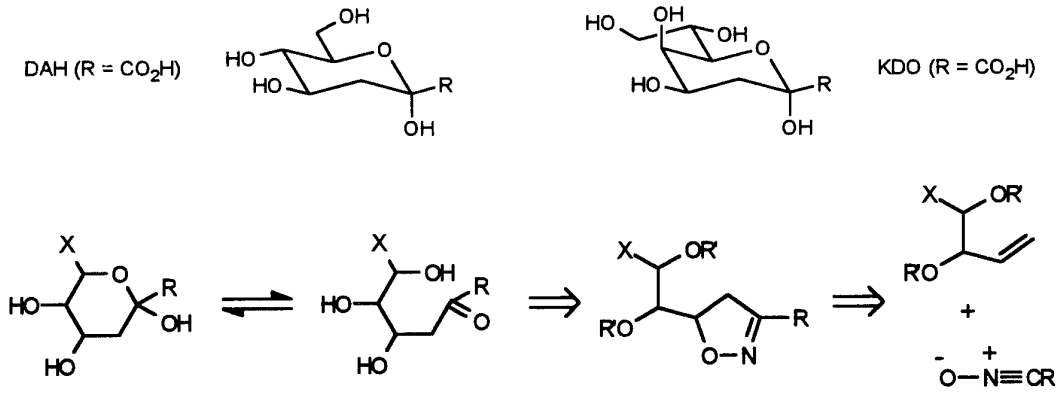
1,3-Dipolar cycloaddition of nitrile oxides to alkenes yielding 2-isoxazolines is a long established reaction which is a currently the focus of renewed attention as a key step in a synthetic route[1] to various natural products and analogues. The utility of nitrile oxides stems from their ease of generation under mild conditions from readily accessible precursors, the stereochemical control of their reactions with alkenes, and the diversity of functionality obtainable from the resulting 2-isoxazoline cycloadducts. Typically, reductive cleavage of isoxazolines can yield β-hydroxyketones and γ-aminoalcohols (Scheme 1). We have recently described the use of this technique for the synthesis of higher-carbon monosaccharides[2] and carbon-bridged disaccharides.[3]



Scheme 1

We are currently applying this methodology to establish a general route to analogues of 3-deoxy-D-*arabino*-heptulosonic acid (DAH, a key intermediate on the shikimate pathway to aromatic amino acids) and 3-deoxy-D-*manno*-octulosonic acid (KDO, an important component of lipopolysaccharides). The approach adopted (Scheme 2) involves cycloaddition of nitrile oxides to readily accessible carbohydrate alkenes followed by reductive hydrolytic cleavage of the resulting isoxazolines.



Scheme 2

References

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13TH LAKELAND HETEROCYCLIC SYMPOSIUM
GRASMERE, 8-12 MAY 1997

STUDIES OF NOVEL NITRO-SUBSTITUTED NITROGEN HETEROCYCLES

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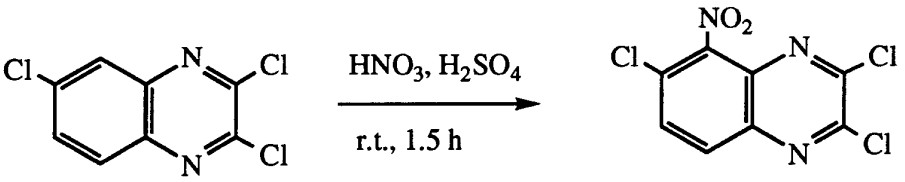
[b]*Department of Chemistry, Brunel University, Uxbridge, Middlesex UB8 3PH, UK*

At DERA we are interested in preparing *Insensitive Energetic Materials.* These usually contain the NO_2 functionality (either C-NO_2, O-NO_2 or N-NO_2). It is proposed to prepare energetic benzodiazines (quinoxalines and quinazolines) functionalised with nitro groups. It is expected that by the incorporation of amino and N-oxide functionalities, insensitivity (thermal and mechanical) can be imparted to these compounds.

The nitration of chloroquinoxaline compounds has been investigated. 2,3-Dichloroquinoxaline was nitrated under a variety of conditions but only breakdown products were observed. The nitration of 2,3,6-trichloroquinoxaline, on the other hand gave the 5-nitro derivative in good yield (**scheme 1**). 2,3-Dihydroxyquinoxaline has been nitrated to give 2,3-dihydroxy-6,7-dinitroquinoxaline[1] which has been converted to the 2,3-dimethoxy derivative. Amination studies, currently incomplete, have indicated that gaseous ammonia is insufficiently reactive towards various chloro- and methoxybenzodiazines and stronger conditions will be necessary.



Scheme 1

The nitration of 2,4-dichloroquinazoline, prepared from benzoylene urea, has been attempted but only breakdown products were observed.

2,4-Diamino-6,8-dinitroquinazoline has been prepared in good yield via the dinitration of 2-methoxybenzonitrile and its subsequent ring closure with guanidine[2]. The oxidation and direct amination of this compound are currently being investigated.

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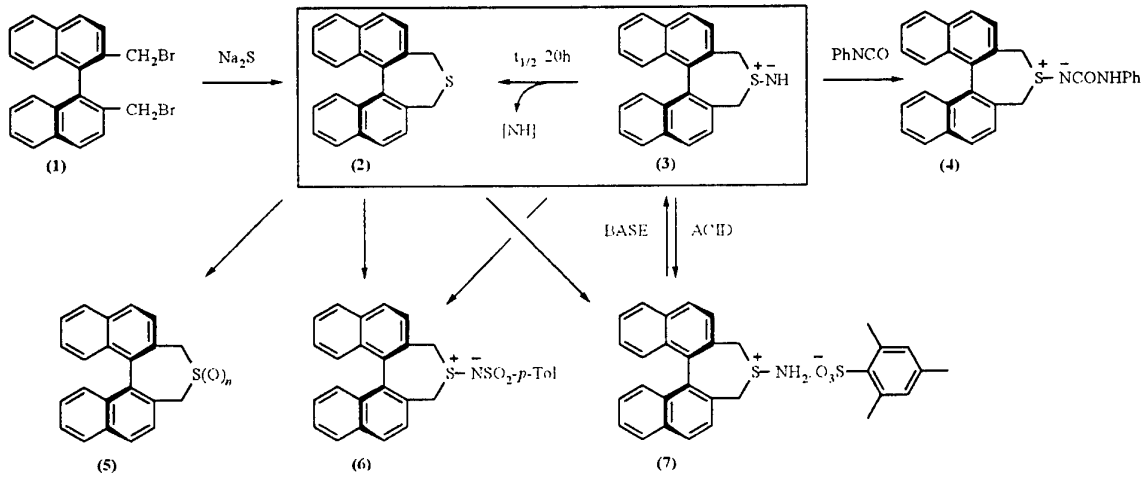
13TH LAKELAND HETEROCYCLIC SYMPOSIUM
GRASMERE, 8-12 MAY 1997

SYNTHESIS OF A NOVEL C_2 SYMMETRIC SULFILIMINE

A. D. M. Curtis,[a] R. McCague,[b] C. A. Ramsden,[a] and M. R. Raza[a]

[a] Keele University, Dept. of Chemistry, Keele, Staffordshire, ST5 5BG, [b] Chiroscience, Cambridge Science Park, Milton Road, Cambridge, CB4 4WE, U.K.

Starting from the known dibromide **(1)** we have prepared the novel binaphthyl sulfide **(2)** (91 %) as a racemic mixture.[1,2] This crystalline sulfide was readily oxidised by sodium perborate to either the sulfoxide **(5**; n=1) or the sulfone **(5**; n=2) using 1 or 2 equivalents of sodium perborate respectively.[3] Reaction of the sulfide **(2)** with mesitylenesulfonylhydroxylamine gave the *S*-aminosulfonium mesitylene-sulfonate salt **(7)** (87 %).[4,5] The "free" sulfilimine **(3)** was too unstable to be isolated but was readily detected by ^{1}H nmr upon treatment of the salt **(7)** with LDA and at ambient temperature it slowly and quantitatively dissociated to give the sulfide **(2)**. The half-life for this reaction (**3** → **2**) is approximately 20 hours. The "free" sulfilimine can be trapped by tosyl chloride leading to the substituted sulfilimine **(6)** which was identical to a sample prepared from the sulfide **(2)** and chloramine-T.[6] The sulfilimine **(3)** gave the derivative **(4)** upon treatment with phenyl isocyanate.[4,5]



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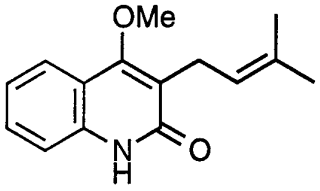
Potential Anthelmintic Compounds based on the Quinoline Alkaloid Atanine

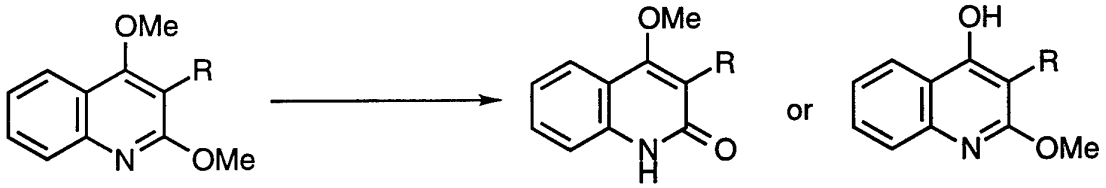
Sharon Rossiter, Keith Jones and Xavier Roset
Department of Chemistry, King's College London, Strand, London WC2R 2LS.

The quinoline alkaloid atanine **1** was recently found to have anthelmintic activity, specifically against the larvae of *Schistosoma mansoni* [1].

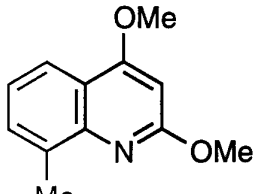


1

Our work is concerned with an efficient synthesis of atanine which can be modified to produce a wide range of analogues for bioassay.
One area we have been exploring is the selective demethylation of 2,4-dimethoxyquinolines.



8-Substituted quinolines have shown some interesting biological activity, for example the trisubstituted quinoline **2**.



2

Progress in these areas will be presented, as well as preliminary bioassay data for compounds prepared so far.

1. Perrett S., Whitfield P.J., *Planta Medica*, 1995, **61**, 276.

NEW HETEROCYCLIC ACYL ANION EQUIVALENTS

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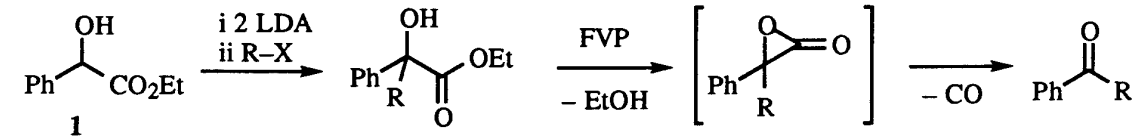
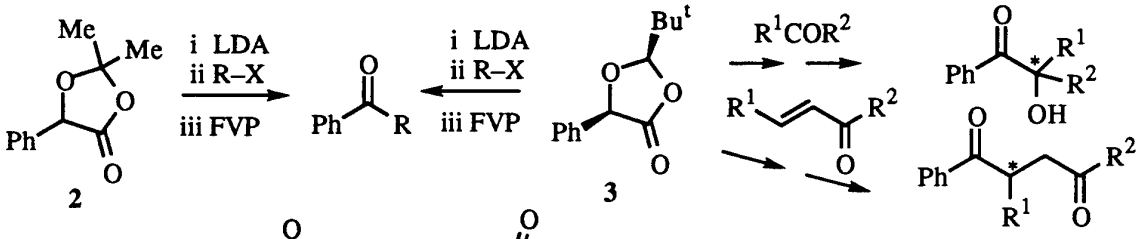
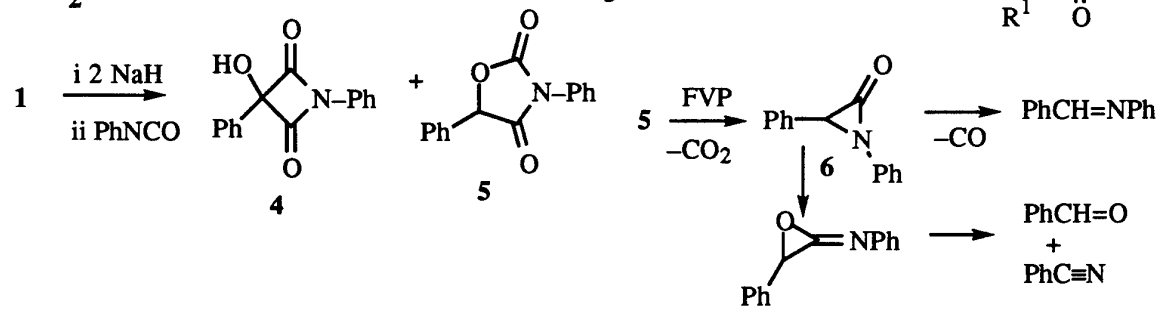
We recently reported that ethyl mandelate **1** may act as an acyl anion equivalent by α-alkylation followed by flash vacuum pyrolysis (FVP) which probably proceeds by way of an α-lactone as shown to give the ketones.[1] This has now been extended to the dioxolanones **2** which only require one equiv. of base and eliminate acetone and CO upon FVP. This is very fortunate since it opens the way to chiral acyl anion equivalents using the principle of self-regeneration of stereogenic centres extensively developed by Seebach.[2] Thus, the pivalaldehyde derived dioxolanone **3** can also be α-alkylated and upon FVP give the ketones. By using electrophiles such as carbonyl compounds and enones where a new stereocentre is formed this should allow asymmetric synthesis as shown and the latest results will be presented.



some examples R = D, Me, Et, Pr^i, Bu^n, c-C_6H_{11}





As an extension to this study, alkylation of the dianion of ethyl madelate with PhNCO was found to give the novel 3-hydroxyazetidine-2,4-dione **4** and the oxazolidinedione **5** separable by crystallisation. FVP of **5** proceeds by loss of CO_2 to give the α-lactam **6** and its decomposition products as shown.

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THE IODOBENZENE DIACETATE OXIDATION OF BIOACTIVE PHENOLS

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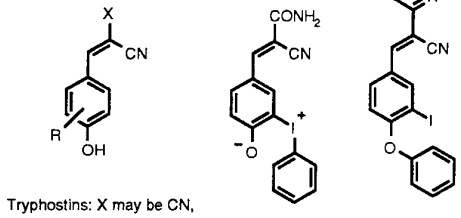
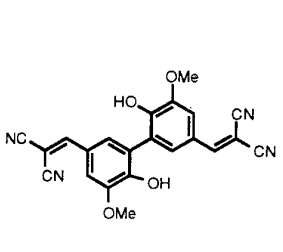
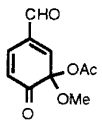
Phenols such as tryphostins and 2-[hydroxyphenyl]benzothiazoles inhibit enzymes such as the epidermal growth factor tyrosine kinase and retard the *in vitro* growth of breast cancer cells. Oxidation of these compounds may be a critical bioactivation pathway required for biological activity and explain the observed time delay between their administration and effect on cell growth[1]. Consequently, the hypervalent iodine compound iodobenzene diacetate has been used to examine the behaviour of these compounds and related structures under oxidising conditions.

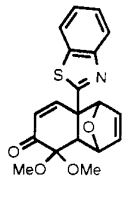
Considerable diversity can be generated from this type of phenolic oxidation. The reaction is highly dependant upon the reaction conditions, namely the choice of solvent, temperature, pH, concentration of reactants and stoichiometry of oxidising agent. The substitution pattern of the phenols, which usually possess an electron-withdrawing group, also has a critical influence on the course of the reaction.

From 4-substituted-phenols, phenyliodiniophenolates (1) and iodophenoxybenzenes (2) can be generated. 4-Substituted-guaiacols can be oxidatively coupled in acetonitrile to give 2,2'-dihydroxy-3,3'-dimethoxybiphenyls (3) or converted to 2-acetoxy-2-methoxy-3,5-cyclohexadienones (4) in acetic acid, which can aromatiseunder acid conditions to give 3-acetoxy-4-substituted-guaiacols. Unstable ortho-quinone monoketals produced from these phenols may be trapped using Diels-Alder reactions. Dienes or dienophiles may be used as trapping reagents to give cycloadducts such as (5).









The growth inhibitory activity of these compounds has been evaluated in various breast cancer cell lines and in the NC1 human tumour in vitro cell line screen. Generally they appear to be equipotent or slightly more potent than their phenolic precursors.

References

1. Faaland CA. et al. *Molecular & Cell. Biol.* **1991**, 11, 2697-2703.

A Tandem Cycloadition Strategy for the Synthesis of (-)-Histrionicotoxin

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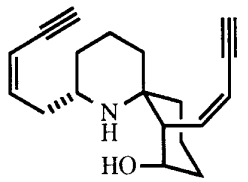
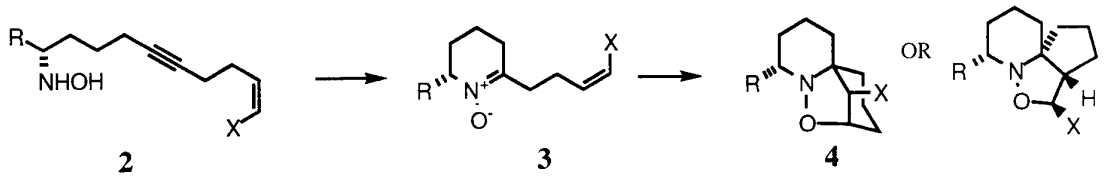
Histrionocotoxin (**1**) is a member of a group of toxic alkaloids isolated[1] in minute quantities from the skin of the poison-arrow frog *Dendrobates histrionicus*. It posses the singular azaspiro[5,5]undecane ring framework, the first such example known to occur in nature, together with the unusual *cis*-enyne side chains. The compound is a potent noncompetitive inhibitor of the nicotinic acetylcholine receptors[2] and thus affects the neuromuscular signalling pathway, which may be of potential therapeutic significance.

This combination of significant biolocal activity, unusual structural features and rarity of the natural source makes **1** an attractive synthetic target.[3]



Histrionicotoxin (1)

A novel approach (scheme) to the construction of the fairly complex azaspiro heterocycle utilises an intramolecular cycloaddition of a suitably functionalised nitrone (**3**) carrying sterically undemanding vinyl substituents (eg. C≡C or C≡N).[4] This nitrone is itself generated from an acyclic precursor (**2**), bearing a single stereocentre, *via* an intramolecular hydroxylamine-alkyne cyclisation.[5] The poster will describe this and efforts to incorporate a suitable group 'X' which will enable the cycloaddition to occur in the desired regiochemical manner, affording a ring system (**4**) which may be elaborated to **1**.



2 **3** **4**

Scheme

References.

1 J. W. Daley, I. Karle, C. W. Myers, T. Tokuyama, J. A. Waters and B. Witcop, *Proc. Nat. Acad. Sci, USA*, 1971, **68**, 1870.
2 J. W. Daley, H. M. Garraffo and T. F. Spando, *The Alkaloids*, ed. G. A. Cordell; Academic Press: 1993; vol. 43; pp185.
3 Two syntheses have been reported. See S. C. Carey, M. Aratani and Y. Kishi, *Tetrahedron Lett.*, 1985, **26**, 5887 and G. Stork and K. Zhao, *J. Am. Chem. Soc.*, 1990, **112**, 5875.
4 For recent review of this chemistry see M. Frederickson, *Tetrahedron, 1997*, **53**, 403.
5 M. E. Fox, A. B. Holmes, I. T. Forbes and M. Thompson *J. Chem. Soc. Perkin Trans. I*, 1994, 3370.

THE PHOTOCHEMISTRY OF α- AZIDOCINNAMATES - A REINVESTIGATION

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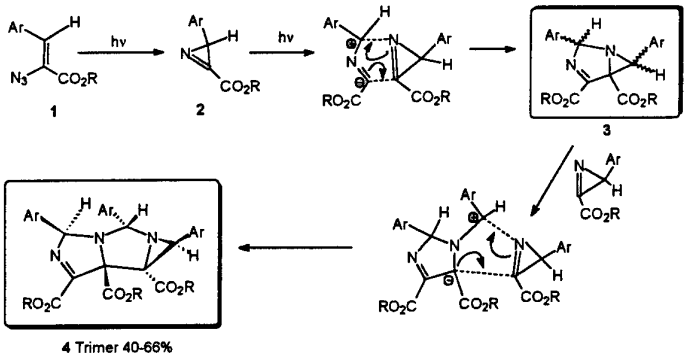
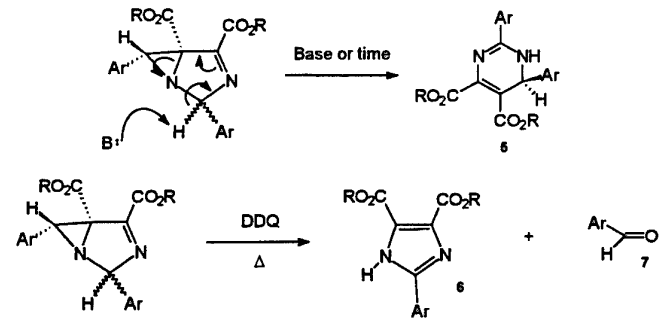
α- Azidocinnamates are versatile intermediates, yielding indoles efficiently on thermolysis[1] via isolable azirines, and novel trimers in a stepwise and efficient manner by photolysis using Quartz equipment[2]. The latter reaction was intensely studied by Rees *et al* who showed that it proceeded by generation of a 1,3-dipole from the azirine **2** which underwent cycloaddition to give a dimer **3** (not isolated) followed by a second cycloadditon to produce the trimer **4** (Scheme 1), whose structure and stereochemistry was confirmed by X-ray crystallography.



Scheme 1

During studies of triplet-sensistised photolyses we re-examined the photolysis of various azidocinnamates in acetone solution with a view to observing alternate chemistry, mediated by radical pathways. To our surprise a rapid clean and high yielding reaction ensued to give dimeric products, which we have shown conclusively to be the stereoisomeric intermediates **3** predicted by Rees and co-workers. More surprisingly, the same products formed when a *non-sensitised* photolysis was conducted in Pyrex equipment, either using the Rayonet reactor or more effectively using our novel simple reactor (Rowe-Meth-Cohn-flask).

Further investigation of the dimers showed slow rearrangement on standing or more rapid rearrangement with addition of base to the pyrimidine **5**. Oxidative treatment of the isolated dimers or the mixture of both diastereoisomers with DDQ produced the simple imidazole **6** and the corresponding araldehyde **7**.



Scheme 2

References

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13TH LAKELAND HETEROCYCLIC SYMPOSIUM

GRASMERE, 8-12 MAY 1997

SYNTHESIS OF INDOLMYCIN ANALOGUES WITH NOVEL HETEROATOM VARIATION IN THE 2-AMINOOXAZOLIN-4-ONE RING

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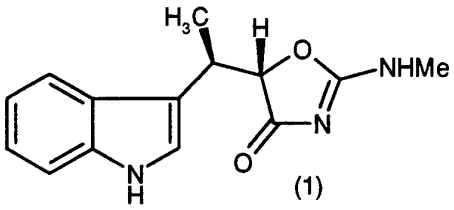
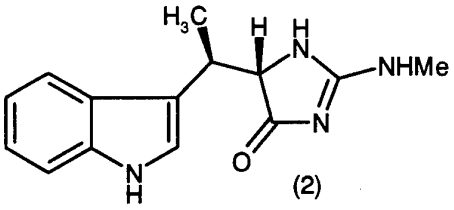
Recent studies of the structure activity relationships between analogues of the tryptophanyl tRNA synthetase inhibitor indolmycin (1) have indicated that both the antibacterial and enzyme inhibitory properties are extremely sensitive to substitution.[1] Modification of the ethyl group bridging the aromatic and oxazolinone rings has been reported and replacement of the indole moiety by other aromatic groups also investigated.[2] Here we report synthetic studies aimed at modifying the heteroatoms and substitution pattern in the oxazolinone ring.[3]



(1)



(2)

The 2-aminooxazolinone ring of indolmycin is structurally ambiguous with at least four possible geometrical isomers and tautomeric forms, two of which are observed in solution. In order to help determine which form is important for binding to tryptophanyl tRNA synthetase, a series of analogues were targeted in which substitution on this ring was designed to alter the tautomeric ratios. One compound prepared during this work (2) represents the first reported stereoselective synthesis of a 5-substituted 2-alkylaminoimidazolin-4-one heterocycle.

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2. D.R. Witty, G. Walker, J.H. Bateson, Peter J. O'Hanlon and R. Cassels, *Bioorganic & Medicinal Chemistry Letters*, 1996, **6(12)**, 1375; D.R. Witty, G. Walker, J.H. Bateson, P.J. O'Hanlon, R. Nicholas and R. Ford; submitted for publication.

3. A more detailed account of this work will be described in a paper currently in preparation for publication.

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