Grasmere '97
The Thirteenth Lakeland Symposium on
Heterocyclic Chemistry

Grasmere Village, Cumbria, UK
8th-12th May, 1997
Grasmere '97
Heterocyclic Group of The Royal Society of Chemistry

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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:

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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
1915-2000  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*

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<th>Institution</th>
<th>Topic</th>
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<tr>
<td>09.15–10.15</td>
<td><em>Professor E C Taylor</em></td>
<td><em>Princeton University</em></td>
<td>Novel Inhibitors of Folate-Dependent Enzymes as Antitumor Agents</td>
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<td>10.15–10.45</td>
<td><em>Professor J M Bakke</em></td>
<td><em>Norwegian University of Science and Technology, Trondheim</em></td>
<td>A New Nitration Method for Pyridine</td>
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<td>11.15–11.45</td>
<td><em>Professor C-K Sha</em></td>
<td><em>National Tsing Hua University</em></td>
<td>Anionic and Radical Cyclisation Approaches to Tetrahydro-3-furanone and 3-Pyrrolidinone: Application to Total Syntheses of Heterocyclic Natural Products</td>
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<tr>
<td>11.45–12.45</td>
<td><em>Professor F A Davis</em></td>
<td><em>Temple University</em></td>
<td>Asymmetric Synthesis and Applications of Heterocycles using Sulfinimines (Thiooxime S-Oxides)</td>
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**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

   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 Pounellec

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 Analognes with Novel Heteroatom Variation in the 2-Aminoazoxazolin-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) NaN₃ in aq. acetone. (ii) Cl(CH₂)₂C=CH at 60°C. (iii) Boiling diphenyl ether (259°C).

2. Difficult:


3. Quirky:

(i) In CH₂Cl₂ 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.

![Chemical structure](image)

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-acyltetrameric acids, e.g. tenuazonic acid 4, which shows antibacterial and antiviral activity, and the 3-acyl-4-hydroxypryridone natural product group 5, via the bicyclic isoxazole-fused lactams 3 as 'masked' non-polar building blocks.

![Chemical structure](image)
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\(^1\) and put into practice on a multigram scale.

![Chemical structures 1 and 2]

Our synthetic interest coupled with the biological potential 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) and accordingly peripherally substituted pyrimidines (4) were identified as target starting materials.

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 R² ≠ H instead of the proposed condensation product reaction between the α-formylchloropyrimidine (5) and the amine (6) lead to the imidazopyrimidinone (7).

The influence of the substituent X, on the alkene tether of (4), in determining the outcome of the reaction of (4) with NH₂OH 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.

References:
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 acceptor¹, or 1,2-addition to the enone carbonyl can be effected by choosing the proper conditions². The C-5 position of the heterocycle is susceptible to electrophilic substitution³, and alkylation at C-3 can be carried out via the enolate⁴. Due to A¹,³ strain, the C-2 substituent of 1 is forced axial, providing a conformational bias in the molecule⁵. 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-methoxypyridine⁶. We have reported that dihydropyridones 1 are useful intermediates for the stereoselective preparation of several racemic alkaloids⁷. Recently, we enhanced the scope of this chemistry by describing a method for preparing heterocycles 1 enantiomerically pure by the addition of Grignard reagents⁸ or metallo enolates⁹ to homochiral 1-acylpyridinium salts. This asymmetric modification has been useful for the enantioselective preparation of various alkaloids⁹. 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

REFERENCES


SYNTHESIS AND REACTIONS OF NEW ELECTROPHILIC AND NUCLEOPHILIC HETEROYCIC BUILDING BLOCKS

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

We have recently developed efficient methodology for the generation of optically thiurium ions (1) and aziridinium ions (2), from the corresponding 2,3-epoxy sulfides or 2,3-epoxyamines respectively (scheme 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).

\[
\begin{align*}
\text{Reagents and conditions: i) TMSOTf, CH}_2\text{Cl}_2, -78\, ^{\circ}\text{C} \\
\end{align*}
\]

\[
\begin{align*}
\text{Scheme 1.}
\end{align*}
\]

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 thiurium (1) and aziridinium (2) ions with nucleophilic nucleoside base equivalents. 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 regiosomers.

\[
\begin{align*}
\text{Scheme 3.}
\end{align*}
\]
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. 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.](image)

References.


CHIRAL OXAZOLINES AS LIGANDS IN ASYMMETRIC CATALYSIS

Andreas Pfaltz
Max-Planck-Institut für Kohlenforschung
Kaiser-Wilhelm-Platz 1, D-45470 Mülheim an der Ruhr, Germany

C₂-Symmetric bisoxazolines 2, which have evolved from our work on chiral semicorrins 1, are highly effective, versatile ligands for asymmetric catalysis. Copper complexes 2 (M = Cu)\textsuperscript{1}, e.g., have been successfully applied as catalysts for enantioselective cyclopropanation\textsuperscript{1} or allylic oxidation of olefins.\textsuperscript{2} For a number of metal-catalyzed processes, non-symmetric phosphino-oxazolines or mercapto-oxazolines have proven to be superior to C₂-symmetric bidentate nitrogen ligands. Enantioselective reactions based on catalysts of type 3 (M = Pd, W) or 4 (M = Cu)\textsuperscript{1} include allylic substitution,\textsuperscript{3,4} Heck-type reactions,\textsuperscript{5} and 1,4-addition of Grignard reagents to enones.\textsuperscript{6} All these ligands are readily prepared in high enantiomeric purity from amino alcohols.

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, $\beta$-hydroxyamides, aminoacids. The lecture will also discuss a new type of rearrangement allowing the ortho-alkylation of aryl- and heteroaryl acetic acids.
SYNTHETIC APPLICATIONS OF UMPOLED VILSMEIER REAGENTS
Otto Meth-Cohn, Simon Goon and Ying Cheng
Chemistry Department, University of Sunderland, Sunderland SR1 3SD, UK
[otto.meth-cohn@sunderland.ac.uk]

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 chloroaminocarbenes (2). This reaction proceeds effectively even in POCl₃ 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 POCl₃ solution a trimer (4) is formed with pyridine as the base while aliphatic amines result in a tetramer¹ (5). A one-pot route from formanilides to isatins will also be described² (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.

References:
1. Y. Cheng, S. Goon and O. Meth-Cohn, Chemical Communications, 1996, 1395
CHIRAL BASE-MEDIATED ASYMMETRIC DESYMMETrISATION –
A POWERFUL TOOL IN ORGANIC SYNTHESIS

Simon E. de Sousa, Peter O'Brien and Pierre Poumellec
Department of Chemistry, University of York, Heslington, York Y01 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.

Scheme 2: The Strategy Works!

Thus, epoxide trans-5 gave allylic alcohol (1S,4R,5S)-6 with 76%ee and epoxide cis-5 gave allylic alcohol (1S,4S,5R)-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 aziridinium ion 11 which is opened regio- and stereospecifically at the benzylic position by methylamine. This is essentially a one-pot protocol which is high yielding and technically easy.

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.

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

References:
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 constructed 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.
HETERO CYCLIC PUSH-PULL MOLECULES AS ORGANIC COMPONENTS FOR ADVANCED NLO MATERIALS

Giorgio Pagani

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 manufacturing companies feel that substantial improvements are needed in order to consolidate and possibly 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.

\[
\begin{align*}
\text{Me}_2N-\text{Ph}-\text{Ph} & \quad \text{Me}_2N-\text{Ph}-\text{Ph} \\
1 & \quad 1'
\end{align*}
\]

\[
\begin{align*}
\text{ground state: neutral, aromatic} & \quad \text{excited state: dipolar, quinoid}
\end{align*}
\]

\[
\begin{align*}
\text{N} \quad \text{X} \quad \text{N} & \quad \text{N} \quad \text{X} \\
2 & \quad 2'
\end{align*}
\]

\[
\begin{align*}
\text{R} \quad \text{N} \quad \text{R} & \quad \text{R} \quad \text{N} \\
3 & \quad 3'
\end{align*}
\]

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
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.

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 \( \beta \) 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.

REFERENCES


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.

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.

References
NOVEL INHIBITORS OF FOLATE-DEPENDENT ENZYMES AS ANTITUMOR AGENTS.

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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'-deoxycytidine-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.
A NEW NITRATION METHOD FOR PYRIDINE

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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. We have recently reported the successful nitration (yields 50 - 70 %) of pyridine and substituted pyridines by the use of dinitrogen pentoxide (N₂O₅, DNP) in liquid sulfur dioxide. We have also discussed possible reaction mechanisms for the reaction.

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 NO₂BF₄ 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.

\[
\begin{align*}
\text{Y} & \quad + \quad \text{O}_2\text{NX} \quad \xrightarrow{\text{CH}_3\text{NO}_2} \quad \text{Y} \quad \xrightarrow{\text{Nu/H}_2\text{O}} \quad \text{Y} \\
\text{NO}_2 & \quad \text{X} \quad \text{NO}_2 & \quad \text{Nu} & \quad \text{NO}_2 \\
\text{1} & \quad \text{2} & \quad \text{3}
\end{align*}
\]

\[Y = \text{H, CH}_3, \text{CH}_3\text{CO} \quad 20 - 70 \%
\]

ANIONIC AND RADICAL CYCLIZATION APPROACHES TO TETRAHYDRO-3-FURANONE AND 3-PYRROLIDINONE: APPLICATION TO TOTAL SYNTHESSES OF HETEROCYCLIC NATURAL PRODUCTS

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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.

\[
\begin{align*}
\text{O} & \quad \text{Li} \\
\text{Y} & \quad \longrightarrow \\
\text{X} & \quad \text{O} \\
\text{N(OMe)Me} & \quad \text{OEt}
\end{align*}
\]

1: \( X = O \)
2: \( X = \text{NR} \)

\[
\begin{align*}
\text{Ph} & \quad \text{X} \\
\end{align*}
\]

X = NR

3
Hexahydrobenzofuran unit of Avermectins

4
Haemanthamine
ASYMMETRIC SYNTHESIS AND APPLICATIONS OF HETERO CYCLES USING SULFINIMINES (THIOOXIME S-OXIDES)

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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 sulfanamide 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.

\[
\begin{align*}
1 \xrightarrow{\text{M-Z}} & \quad 2 \quad \text{or base} \quad 3
\end{align*}
\]

We devised a simple "one pot" procedure for the asymmetric synthesis of sulfinimines 1, making these compounds readily available for the first time. This protocol involves reaction of lithium bis(hexamethyldisilazane) with commercially available (-)- or (+)-menthol (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. 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.
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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{5} Addition of organometallic reagents to 6 occurs in a syn stereospecific manner affording the previously unavailable 3,3-unsymmetrical disubstituted aziridine 7.

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References
THE BIRCH REDUCTION OF NITROGEN-CONTAINING HETEROCYCLES

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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). 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-Dehydropoline derivatives were obtained by quenching the reaction with ammonium chloride.

\[ \text{Scheme 1} \]

R = Me, Bu, 'Bu, H etc. Yields 75-87%

* Structure proven by X-ray crystallography
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). 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.

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

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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 initiated 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.

RECENT DEVELOPMENTS IN COMPUTER AIDED DESIGN OF EFFECT CHEMICALS

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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 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 inhibitor design will be presented.
NOVEL INDOLE CHEMISTRY IN THE SYNTHESIS OF NATURAL PRODUCTS

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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.

\[ \text{1} \quad \text{NO}_2 \quad \text{SO}_2 \text{Ph} \quad \xrightarrow{\text{C=N-CH}_2\text{CO}_2\text{Et (2)}} \quad \xrightarrow{\text{DBU}} \quad \text{85\%} \quad \text{3} \quad \text{CO}_2\text{Et} \]

PhO\text{S}_2N
SOME APPLICATIONS OF PALLADIUM AND COBALT TO HETEROCYCLE SYNTHESIS

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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 \(\pi\)-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.

A RADICAL APPROACH TO THE SYNTHESIS OF MITOMYCIN

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The mitomycins are a group of antibiotics all containing the common structure 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.\textsuperscript{1,2}

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

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

References
Calix[4]resorcinarenes have been used profitably by several workers, notably Cram, Reinhoudt and Aoyama.\textsuperscript{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.\textsuperscript{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 \textsuperscript{1}H NMR analysis of the octabutyrates. The structure of compound (3a) was proved \textit{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.

\textbf{References:}
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-acyltetrameric acids such as tenuazonic acid 2, which shows antibacterial and anti-viral activity, and the pyridone illicicolin H.

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<sub>1</sub> 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.

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.

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.
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

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.

References
†This work was supported by the Cancer Research Campaign
A DECONJUGATION - ALKYLATION ROUTE TO NOVEL ANALGESICS

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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 its 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 ocdhydroisoquinolones 5 by deconjugation - alkylation of the parent isoquinolone 4. A second product, the γ-alkylated product 6 was also formed as the minor constituent.

Reduction of these should then lead to the biologically active molecules 7 and 8.
THE FIRST PREPARATION OF EPISULFONES FROM EPISULFIDES:
OXIDATION USING OXONE®/TRIFLUOROACETONE

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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 conditions2 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

![Diagram]

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).
HETEROCYCLIC ENEDIYNES AS PROBES OF BIOMOLECULE FUNCTION
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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.\textsuperscript{1} In addition to inflicting lesions in DNA, which in turn may activate suicide repair pathways, \textsuperscript{2} a number of enediynes have been reported to induce protein degradation and agglomeration.\textsuperscript{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 \textsuperscript{3}, which incorporate a minimum effective subunit required for a particular biological response, their subsequent synthesis from diyls \textsuperscript{2} can be envisioned, via controlled cycloaromatization of enediynes \textsuperscript{1}. Moreover, if the biological targets of \textsuperscript{3} are defined, the effects of \textsuperscript{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 \textsuperscript{2} could also be performed, to yield analogs of target \textsuperscript{3} i.e. \textsuperscript{4}. The pursuit of these studies has already resulted in new developments in enediyne chemistry, and in the identification of new affinity cleavage systems.

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 \textsuperscript{5} (X=Hal), when converted to the corresponding lithio
halocarbenoid species, undergo coupling reactions to produce haloalkynes 6 (Scheme 2). Under mild conditions, these species undergo in situ elimination to give enediynes 7 directly.

Scheme 2. Carbenoid insertion-elimination route to enediynes

\[ \begin{align*}
R_1 & \rightarrow \text{LiHMDS} \rightarrow \text{HMPA} \\
& \text{-78 to -45°C} \\
\end{align*} \]

A variety of substituted linear enediynes are available using this process, and, via the intramolecular variant, both carbocyclic and heterocyclic systems. 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, the human estrogen receptor (hER), and the aryl hydrocarbon receptor (AhR). Recent developments in these areas will be highlighted, together with other ongoing applications.

References
A RADICAL ROUTE TO THE MONOTERPENE ALKALOIDS OXERINE AND ACTINIDINE

Andrea Fiumana, Keith Jones and Maria Luisa Escudero Hernandez
Department of Chemistry, King's College London, Strand, London WC2R 2LS. UK.

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.

![1 and 2]

References
ALTERNATING \( \pi \)-ELECTRON DEFICIENT: \( \pi \)-EXCESSIVE HETEROCYCLIC 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 \( \pi \)-electron deficient: \( \pi \)-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.

\[
\text{CHO} \quad \text{CH} = \text{CHCOR} \quad \text{thiazolium ylide or \text{CN}^+} \\
\]

\[
\text{CHO} \quad \text{CHCOR} \quad \text{thiazolium ylide or \text{CN}^+} \\
\]

\[
X = \text{O, S, NH, NR} \\
\]

1. \( R = \text{Me or Ph}; \)

2. \( R = 2, 3 \text{ or 4-pyridyl} \)

3. \( R = \text{Me, Ph, 2-pyridyl} \)

\[
\text{R} \quad \text{R} \quad \text{R} \quad \text{R} \\
\]

The compounds are best characterised by their \( ^{13} \text{C} \) 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 \( \text{O} > \text{S} > \text{NR} > \text{NH} \). This can be interpreted in terms of steric and, for \( X = \text{NH} \), H-bonding shielding of the pyridine N atom. Similarly, quaternisation of 3-(2-pyrrolyl)pyridazine occurs on \( \text{N}^1 \) and not \( \text{N}^2 \) of the pyridazine ring.\(^4\)\(^5\)

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


School of Chemical Sciences, University of East Anglia, Norwich, NR4 7TJ, UK
Departamento de Química Organica, Universidad de Alcalá de Henares, E-28871, Madrid, Spain

As part of a programme to prepare and evaluate the biological 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 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

TROST'S LIGANDS FOR PALLADIUM(0) CATALYZED
ASYMMETRIC ALYLYC 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 carbors;\(^3\) aristeromycin;\(^3\) (+)-pancratistatin;\(^4\) N-phthalimido-protected vinyl glycino\(^5\) 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.

References.

APPRAOCHES TO OPTICALLY ACTIVE N-(2-AMINOETHYL)HYDROXYLAMINES 
as precursors for heterocyclic homochiral nitrones

Jason N Martin and Raymond C F Jones

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 benzoyleformic acid, from 2-bromoacetophenone, and from N-benzylglycine will be outlined.2

2. We thank EPSRC, SB Pharmaceuticals and Dr Paul S Smith for helpful discussions and financial support.
A MILD ROUTE TO HETEROCYCLIC ACETIC ACIDS USING SODIUM PERBORATE TETRAHYDRATE

N. Morrow, a C.A. Ramsden, a B.J. Sargent, b C.D. Wallett, a

a Department of Chemistry, Keele University, Keele, Staffordshire, ST5 5BG, U.K.
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, and we have now demonstrated that this methodology is applicable to a variety of aromatic and heteroaromatic pyruvic acid derivatives.

![Chemical Structures]

Table: Oxidation of Aromatic Pyruvic Acids using Sodium Perborate Tetrahydrate

<table>
<thead>
<tr>
<th>Ar</th>
<th>Yield (%)</th>
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<td>2-(1-Methyl-5-nitroimidazolyl</td>
<td>81</td>
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<tr>
<td>2-Thienyl</td>
<td>68</td>
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<tr>
<td>2-Pyridyl</td>
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<td>4-Hydroxyphenyl</td>
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References

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 Santafanios, 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 resemblance, 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 tendency 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-alkylamines 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.

CHIRAL BASE-MEDIATED DESYMMEtRISATION OF SUBSTITUTED meso-CYcLOHEXENE OXIDES
Simon E. de Sousa, Peter O’Brien and Pierre Poumellec
Department of Chemistry, University of York, Heslington, York Y01 5DD UK

Epoxides can be transformed into optically active allylic alcohols using chiral versions of LDA. 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 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 aziridinium ion 5 which is opened regio- and stereospecifically at the benzylic position by methylamine.

![Chemical reaction diagram]

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 (1S,4R,5S)-8 with 76% ee in 93% yield. Subsequent oxidation afforded enantiomerically enriched enone (4R,5S)-9, a potentially useful chiral building block.

![Chemical reaction diagram]

Reagents: (i) 1.3 eq (R)-6, 1.3 eq BuLi, THF, 0 °C → rt; (ii) 1.3 eq PDC, CH₂Cl₂, rt, 4 h

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

Paul Allen,* Michael B. Gravestock,² R. Michael Paton* and Christine J. Todd*  

* Department of Chemistry, The University of Edinburgh, West Mains Road, Edinburgh EH9 3JJ, UK  
² Zeneca Pharmaceuticals, Alderley Park, Macclesfield, Cheshire SK10 4TG, UK

1,3-Dipolar cycloaddition of nitrile oxides to alkenes yielding 2-isoxazolines is a long established reaction which is currently the focus of renewed attention as a key step in a synthetic route¹ 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 \( \beta \)-hydroxyketones and \( \gamma \)-aminoalcohols (Scheme 1). We have recently described the use of this technique for the synthesis of higher-carbon monosaccharides² and carbon-bridged disaccharides.³

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.

References
At DERA we are interested in preparing Insensitive Energetic Materials. These usually contain the NO₂ functionality (either C-NO₂, O-NO₂ or N-NO₂). 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-dinitroquinoxaline¹ 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](image)

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 guanidine². The oxidation and direct amination of this compound are currently being investigated.

References
SYNTHESIS OF A NOVEL C₂ SYMMETRIC SULFILIMINE

A. D. M. Curtis, R. McCague, C. A. Ramsden, and M. R. Raza

Keele University, Dept. of Chemistry, Keele, Staffordshire, ST5 5BG, 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-aminosulphonium mesitylene-sulfonate salt (7) (87%). ⁴ ⁵ The "free" sulfilimine (3) was too unstable to be isolated but was readily detected by ¹H 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

References
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*.

![Chemical Structure of Atanine 1](Image)

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.

![Chemical Structures of 2,4-Dimethoxyquinolines](Image)

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

![Chemical Structure of Trisubstituted Quinoline 2](Image)

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

NEW HETERO CYCLIC ACYL ANION EQUIVALENTS

R. Alan Aitken* and Andrew W. Thomas

School of Chemistry, University of St. Andrews, St. Andrews, Fife, KY16 9ST, UK

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 dioxolane 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.

As an extension to this study, alklylation of the dianion of ethyl mandelate 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 CO₂ to give the α-lactam 6 and its decomposition products as shown.

References
THE IODOBENZENE DIACETATE OXIDATION OF BIOACTIVE PHENOLS

G. Wells and M.F.G. Stevens
Cancer Research Laboratories, University of Nottingham, University Park, Nottingham.
NG7 2RD

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. Consequently, the hypervalent iodine compound iodo benzene 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, phenyldiiodophenolates (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 aromatise under 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).

![Chemical structures]

The growth inhibitory activity of these compounds has been evaluated in various breast cancer cell lines and in the NCI1 human tumour in vitro cell line screen. Generally they appear to be equipotent or slightly more potent than their phenolic precursors.

References
A Tandem Cycloaddition Strategy for the Synthesis of (-)-Histrionicotoxin

G. M. Williams and A. B. Holmes*
University Chemical Laboratories, Lensfield Road, Cambridge CB2 1EW.

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 possesses 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)](image)

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 (e.g. C=\(\text{C}\) or C=\(\text{N}\)).\(^4\) 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.

![Scheme](image)

References.
THE PHOTOCHEMISTRY OF α- AZIDOCINNAMATES - A REINVESTIGATION

Nicola J R Williams, Professor Otto Meth-Cohn
Sunderland University, Health Sciences, Fleming Building, Sunderland, SR1 3SD

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 cycloaddition to produce the trimer 4 (Scheme 1), whose structure and stereochemistry was confirmed by X-ray crystallography.

\[
\overset{\text{hv}}{\text{Ar}} \overset{\text{hv}}{\text{H}} \overset{\text{hv}}{\text{N}} = \overset{\text{CO}_{2}R}{\text{Ar}} \rightarrow \overset{\text{Ar}}{\overset{\text{H}}{\overset{\text{N}}{\text{Ar}}} \overset{\text{CO}_{2}R}{\text{Ar}}} \rightarrow \overset{\text{Ar}}{\overset{\text{H}}{\overset{\text{N}}{\text{Ar}}} \overset{\text{RO}_{2}C}{\text{Ar}}} \rightarrow \overset{\text{Ar}}{\overset{\text{H}}{\overset{\text{N}}{\text{Ar}}} \overset{\text{RO}_{2}C}{\text{Ar}}} \rightarrow \overset{\text{Ar}}{\overset{\text{H}}{\overset{\text{N}}{\text{Ar}}} \overset{\text{CO}_{2}R}{\text{Ar}}} \rightarrow \overset{\text{Ar}}{\overset{\text{H}}{\overset{\text{N}}{\text{Ar}}} \overset{\text{RO}_{2}C}{\text{Ar}}} \rightarrow \overset{\text{Ar}}{\overset{\text{H}}{\overset{\text{N}}{\text{Ar}}} \overset{\text{CO}_{2}R}{\text{Ar}}}
\]

Scheme 1

During studies of triplet-sensitised 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 aldehyde 7.

\[
\overset{\text{Base or time}}{\overset{\text{B}}{\text{Ar}}} \overset{\text{RO}_{2}C}{\text{Ar}} \rightarrow \overset{\text{Ar}}{\overset{\text{H}}{\overset{\text{N}}{\text{Ar}}} \overset{\text{RO}_{2}C}{\text{Ar}}} \rightarrow \overset{\text{Ar}}{\overset{\text{H}}{\overset{\text{N}}{\text{Ar}}} \overset{\text{CO}_{2}R}{\text{Ar}}} \rightarrow \overset{\text{Ar}}{\overset{\text{H}}{\overset{\text{N}}{\text{Ar}}} \overset{\text{RO}_{2}C}{\text{Ar}}} \rightarrow \overset{\text{Ar}}{\overset{\text{H}}{\overset{\text{N}}{\text{Ar}}} \overset{\text{CO}_{2}R}{\text{Ar}}} \rightarrow \overset{\text{Ar}}{\overset{\text{H}}{\overset{\text{N}}{\text{Ar}}} \overset{\text{RO}_{2}C}{\text{Ar}}} \rightarrow \overset{\text{Ar}}{\overset{\text{H}}{\overset{\text{N}}{\text{Ar}}} \overset{\text{CO}_{2}R}{\text{Ar}}} \rightarrow \overset{\text{Ar}}{\overset{\text{H}}{\overset{\text{N}}{\text{Ar}}} \overset{\text{RO}_{2}C}{\text{Ar}}} \rightarrow \overset{\text{Ar}}{\overset{\text{H}}{\overset{\text{N}}{\text{Ar}}} \overset{\text{CO}_{2}R}{\text{Ar}}}}
\]

Scheme 2

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

David R. Witty, Catherine L. Wayne, Duncan Morris, John Bateson and Peter O’Hanlon
SmithKline Beecham Pharmaceuticals, New Frontiers Science Park, Coldharbour Road,
The Pinnacles, Harlow, Essex CM19 5AD, United Kingdom

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

![Chemical structures](image)

The 2-aminoxazolinone 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.

References

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

Registered Participants (27.4.97.)

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**Grasmere '97:** Thirteenth Lakeland Heterocyclic Symposium, Grasmere 8 - 12 May 1997

Registered Participants (27.4.97.)

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**Grasmere '97**: Thirteenth Lakeland Heterocyclic Symposium. Grasmere 8 - 12 May 1997

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