JOURNAL OF LABELLED COMPOUNDS AND RADIOPHARMACEUTICALS
J Label Compd Radiopharm 2006; **49**: 377–420.
Published online in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/jlcr.1056

Abstracts

15th International Isotope Society (UK group) Symposium

Synthesis & Applications of Labelled Compounds 2005

F. I. Aigbirhio, E. Alexakis, J. Allen, J.-C. Baron, J. Beech, J. Beyer, J. P. Bloxsidge, N. P. Botting, L. Brichard, N. Bushby, K. Cable, J. C. Clark, L. K. Conway, G. Del Fiore, F. Dollé, G. Ellames, N. Feling, T. Fryatt, T. D. Fryer, A. D. Gee, K. Haajanen, J. R. Harding, S. J. Haswell, M. J. Hickey, D. W. Holt, J. Hooper, A. Johnston, G. Johnston, J. R. Jones, B. Kent, L. P. Kingston, S. L. Kitson, E. Knagg, B. Koch, N. Kuhnert, M. Lang, S. Lang-Fugmann, K. W. M. Lawrie, C. Lemaire, R. J. Lewis, W. J. S. Lockley*, A. Luxen, C. O. Manning, A. N. Mather, P. Meath, J. Passchier, J. A. Perrie, A. Plenevaux, C. Plisson, K. C. Probst, D. O. Rees, L. Rivron, D. Rustidge, M. Rüth, J. M. Schofield, P. Scott, B. Sontag, P. Spiteller, A. V. Stachulski, W. Steglich, A. H. Wadsworth, P. Watts, L. Warburton, P. Weissberg, C. Wiles, D. J. Wilkinson and C. L. Willis

Meeting Summary

The 15th annual symposium of the International Isotope Society's United Kingdom Group took place at the Wellcome Genome Campus, Hinxton, Cambridge, UK on 3rd November 2005. The meeting was attended by around 100 delegates from academia, life sciences and fine chemical companies.

Delegates were welcomed by Dr Ken Lawrie (GlaxoSmithKline, UK). The subsequent scientific programme consisted of oral and poster presentations on isotopic chemistry and applications of labelled compounds, or of chemistry with potential implications for isotopic synthesis. Both short-lived and long-lived isotopes were represented, as were stable isotopes. The symposium programme was divided into a morning and afternoon session chaired by

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Prof. Chris Willis (University of Bristol, UK) and Dr Karl Cable (GlaxoSmithKline, UK), respectively. The meeting was concluded with remarks from Dr Ken Lawrie [GlaxoSmithKline, UK].

This year's symposium had a large attendance from students. Moreover, an excellent level of sponsorship was achieved, and the symposium proved self-financing. The meeting venue again proved very popular. There will be no national meeting next year since the forthcoming IIS triennial symposium will be taking place in Edinburgh on the 16–20th July 2006. The next UK symposium is therefore planned for late 2007.

Meeting Programme

Dr Nigel Botting [University of St Andrews, UK] – *Isotopic Labelling of Lignan Phytoestrogens.*

Prof. Frédéric Dollé [CEA PET Centre, Orsay, France] – *Fluorine-18 Chemistry: A Selection of Recent Advances.*

Prof. Peter Scott [University of Warwick, UK] – *Creating Chiral Metal Centres.*

Mr Laurent Brichard [WBIC, University of Cambridge, UK] – *A Simple Device for the Radiosynthesis of [Carbonyl-^{11}C]amides, Esters and Ketones using Carbon-11 Monoxide.*

Dr Michael Hickey [AstraZeneca Charnwood, UK] – *Tritium-labelling via an Iridium-based Solid-phase Catalyst.*

Prof. Wolfgang Steglich [Ludwig-Maximilians University, Germany] – *Meroterpenoids from Mushrooms, A Colourful Group of Natural Products.*

Dr Joe Schofield [Sanofi-Aventis, France] – *Radio- and Stable-isotope Labelling of SSR591813 – A Nicotinic Partial Agonist.*

Dr Nikolai Kuhnert [University of Surrey, UK] – *Chiral Recognition in Ion Trap Mass Spectrometry using Isotopically Labelled Trianglamine Macrocycles.*

Dr Paul Watts [University of Hull, UK] – *The Application of Micro Reactors for Radiochemical Synthesis.*

Dr Tony Gee [GlaxoSmithKline, UK] – *PET in Drug Discovery and Development.*

Dr Alan Wadsworth [GlaxoSmithKline, UK] – *Stable Isotopic Labelling of Heterocyclic Compounds.*

ABSTRACTS: ORAL PRESENTATIONS

ISOTOPIC LABELLING OF LIGNAN PHYTOESTROGENS

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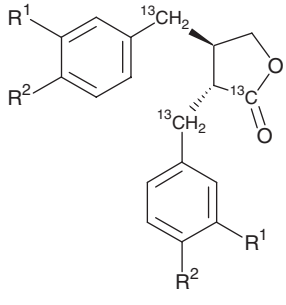
The lignan phytoestrogens are a widely distributed group of plant phenols that are currently being studied for their potential benefits for human health as their consumption has been correlated with lower risks for developing chronic diseases, such as breast cancer and coronary heart disease. In order to better understand the significance of the biological effects of lignans, accurate analysis is important to establish the exposure of the population to the plant lignans through their diet and also in epidemiological studies to investigate the associations between lignan exposure, mammalian lignan levels and disease. A series of lignans with three ^{13}C atoms incorporated into the carbon framework of the molecule have been synthesized as a new generation of internal standards for both GC–MS and LC–MS analysis. The first targets were the plant lignans, matairesinol **1** and secoisolariciresinol **2** which are precursors of the mammalian lignans enterolactone **3** and enterodiol **4** formed by the gut microflora.



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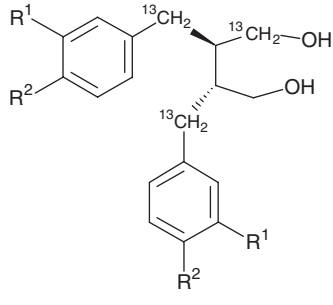
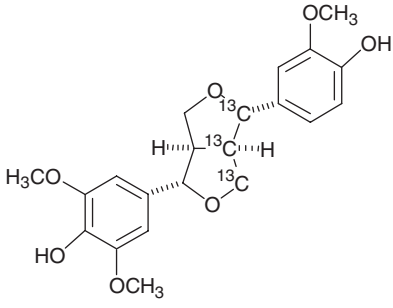


2: $R^1 = OCH_3$, $R^2 = OH$

4: $R^1 = OH$, $R^2 = H$

More recently a second class of lignans, the furofurans, have begun to attract more attention. This includes medioresinol found in rye and sesamin from sesame seeds. These lignans have also been synthesized in ^{13}C-labelled form both to provide internal standards for analytical purposes and also for metabolic studies. The labelled furofuran lignans, [7,8,9-$^{13}C_3$]medioresinol **5** and [7,8,9-$^{13}C_3$]sesamin **6**, were constructed from triply labelled cinnamyl

alcohols, using a key radical cyclization method.



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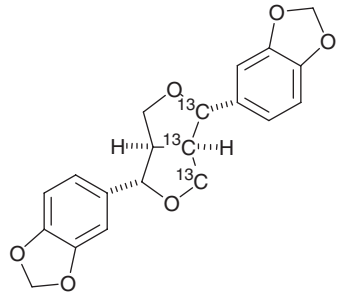

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FLUORINE-18 CHEMISTRY: A SELECTION OF RECENT ADVANCES

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Molecular *in vivo* imaging with the high-resolution and sensitive Positron Emission Tomography (PET) technique requires the preparation of a positron-emitting radiolabelled probe or radiotracer. For this purpose, fluorine-18 is becoming increasingly the radionuclide of choice due to its adequate physical and nuclear characteristics but also due to the successful use in clinical oncology of 2-[^{18}F]fluoro-2-deoxyglucose ([^{18}F]FDG), the currently most widely used PET-radiopharmaceutical and probably the motor behind the growing availability and interest for this positron-emitter in radiopharmaceutical chemistry.

Besides a few exceptions, radiofluorinations involving fluorine-18 of high specific radioactivity (>185 GBq/μmol) had been, until recently, limited to nucleophilic substitutions in *homo*aromatic and aliphatic series with [^{18}F]fluoride.[1–3] Recent advances in fluorine-18 chemistry include the use of moderate specific activity fluorine ([^{18}F]F_2, 3.7–25 GBq/μmol) for aromatic electrophilic substitutions,[4] as well as the use of iodonium salts[5,6] as precursors for labelling, allowing fluorination of electron-rich arenes using *homo*aromatic nucleophilic substitutions and [^{18}F]fluoride. Finally, considering chemical structures showing a fluoropyridinyl moiety, nucleophilic *hetero*aromatic substitution at the *ortho*-position with no-carrier-added [^{18}F]fluoride appears today as the most efficient method for the radiosynthesis of radiotracers and radiopharmaceuticals of high specific radioactivity.[7]

References

1. Kilbourn MR. In *Fluorine-18 Labeling of Radiopharmaceuticals*, Kilbourn MR (ed.). Nuclear Science Series. National Academy Press: Washington, 1990; 1–149.
2. Lasne MC, Perrio C, Rouden J, Barré L, Roeda D, Dollé F, Crouzel C. In *Topics in Current Chemistry. Chemistry of Beta-emitting Compounds based on Fluorine-18*, Krause W (ed.). Springer: Berlin, 2002; 201–211.
3. Welch MJ, Redvanly CS. In *Handbook of Radiopharmaceuticals. Radiochemistry and Applications*, Welch MJ, Redvanly CS (eds). Wiley-Interscience Publishers: New York, 2003; 1–848.
4. Bergman J, Solin O. *Nucl Med Biol* 1997; **24**: 677–683.
5. Pike VW, Aigbirhio FI. *J Chem Soc Chem Commun* 1995; 2215–2216.

6. Ermert J, Hocke C, Ludwig T, Gail R, Coenen HH. *J Label Compd Radiopharm* 2004; **47**: 429–441.
7. Dollé F. *Curr Pharm Design* 2005; **11**: 3221–3235.

CREATING CHIRAL METAL CENTRES

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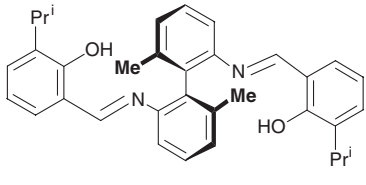
Chiral metal centres[1] are implicated in the mechanisms of several enantioselective catalytic reactions[2] and appear in new classes of chiral solids. The methods by which absolute stereochemistry at the metal may be predetermined have usually either involved complicated organic ligand syntheses or have been relatively inefficient.[3] Studies in this area are complicated by the great structural variety possible in organometallic and coordination compounds and also the range in kinetic stabilities of coordination environments. Accordingly, most studies on chiral metal complexes have involved later transition elements where the rates of topographical exchange are generally slow enough to be studied on convenient experimental timescales. For the early transition metals and f elements, where the rates of exchange are greater, very high levels of thermodynamic discrimination are needed in order to make systems that are of practical value.

The challenge for those concerned with catalysis is to produce complexes in which the metal stereochemistry is selected efficiently while at the same time leaving one or more labile coordination sites where reagent and substrate can be brought together. This has been achieved through the use of multidentate ligands,[4] e.g. **1** and complex **2**; we will address some aspects of the design and synthesis of such coordination environments, including some particular issues which arise when early transition metals and lanthanides are used.



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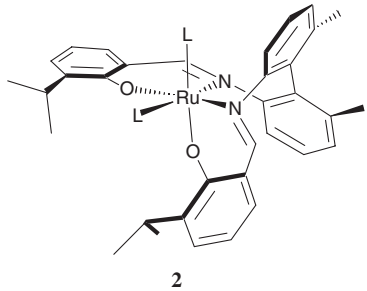

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Bidentate ligands are more readily available and more diverse in nature than multidentate systems. If the aim is to produce chiral metal catalysts then, for, e.g. group 4 metals, this points us toward octahedral complexes of the type $[M(AB)_2X_2]$, where AB is a chiral bidentate monoanionic ligand. While this class of complex can in principle form eight diastereomers, we have recently shown that it is quite possible to design highly diastereoselective systems.

We will describe our studies toward the control stereochemistry at early transition metal centres using a range of chiral bidentate ligands.

Catalytic applications of these compounds include enantioselective cyclopropanation, aziridination, hydroamination and alkene polymerization.

References

1. (a) Brunner H. *Eur J Inorg Chem* 2001; **905**; (b) Brunner H. *Angew Chem Int Ed* 1999; **38**: 1194; (c) Ganter C. *Chem Soc Rev* 2003; **32**: 130; (d) Faller JW, Lavoie AR. *New J Chem* 2003; **27**: 899.
2. (a) Muñiz K, Bolm C. *Chem Eur J* 2000; **6**: 2309; (b) Ashby MT, Halpern J. *J Am Chem Soc* 1991; **113**: 589; (c) Noyori R, Hashiguchi S. *Acc Chem Res* 1997; **30**: 97.
3. (a) Knof U, von Zelewsky A. *Angew Chem Int Ed* 1999; **38**: 302; (b) von Zelewsky A, Mamula O. *J Chem Soc Dalton Trans* 2000; 219.
4. Knight PD, Scott P. *Coord Chem Rev* 2003; **243**: 125.

A SEMI-AUTOMATED DEVICE FOR THE PRODUCTION OF [^{11}C]CO AND ITS SUBSEQUENT USE IN PALLADIUM-CATALYZED CARBONYLATION REACTIONS

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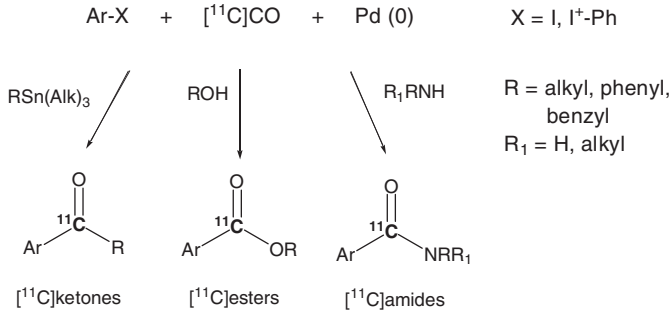
[b]*Cyclotron Research Center, University of Liège, Sart-Tilman B30, B-4000 Liege, Belgium*

During this last decade there have been growing interest in the use of [^{11}C]CO for the labelling of radiopharmaceuticals used in PET imaging.[1–4] Among the different methods developed to introduce this labelling agent into tracers, palladium-catalyzed carbonylation reaction is probably the most versatile for the production of various carbonylated compounds such as amides, esters and ketones (Scheme 1).

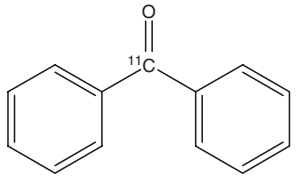


Scheme 1.

The major drawback with the use of [^{11}C]CO is its very low solubility in organic solvents. Therefore, there is a crucial need for the development of a gas handling system to overcome that problem and thus achieve high consumption of produced [^{11}C]CO.[1,5] A simple semi-automated system, using commercial vessel, was designed to realize, under mild conditions, all the synthesis steps: target-produced [^{11}C]CO_2 concentration, Zn reduction of [^{11}C]CO_2 into [^{11}C]CO, its trapping in the reaction vessel (a 10 ml septum-sealed glass vial), radiolabelling and subsequent disposal of unreacted [^{11}C]CO. The whole process takes about 20 min.

A large variety of aromatic ketones, amides and esters were produced with this device in very good radiochemical yields and easily purified on HPLC. Radiochemical yields are decay-corrected and calculated by taking into account the [^{11}C]CO incorporation with respect to [^{11}C]CO production, and

the radiochemical purity of the product. Depending upon the structure, [^{11}C]CO incorporation yields ranging between 80 and 97% were obtained.



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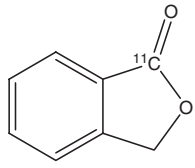

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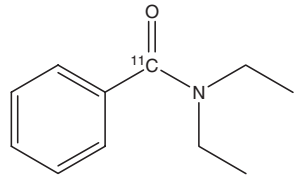

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References

1. Lidström P, Kihlberg T, Långström B. *J Chem Soc, Perkin Trans I* 1997; 2701–2706.
2. Zeisler SK, Nader M, Theobald A, Oberdorfer F. *Appl Radiat Isot* 1997; **48**: 1091–1095.
3. Itsenko O, Kihlberg T, Langstrom B. *J Org Chem* 2004; **69**: 4356–4360.
4. Al-Qahtani MH, Pike VW. *J Label Compd Radiopharm* 2000; **43**: 825–835.
5. Långström B, Kihlberg T. PCT International Application 2002, WO 0102711 A1.

And references cited in these papers.

TRITIUM-LABELLING VIA AN IRIDIUM-BASED SOLID-PHASE CATALYST

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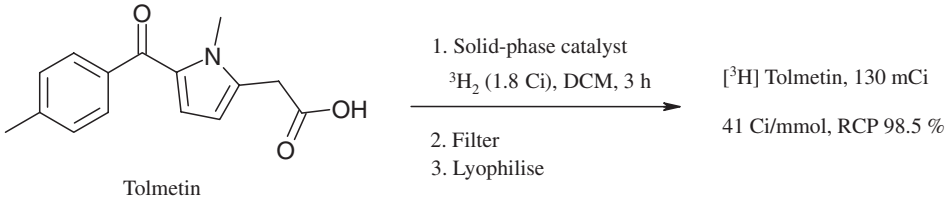
A solid-phase, iridium-based *ortho*-exchange catalyst[1] has been developed as part of a collaboration between the University of Surrey and AstraZeneca Charnwood, UK, which has the aim of producing cleaner, more efficient, systems for tritium and deuterium labelling. The catalyst, which is a solvated polystyrene-bound triphenylphosphine complex of cyclooctadienyliridium(I) hexafluorophosphate, was evaluated with respect to more conventional catalysts such as $CODIr(PPh_3)_2PF_6$ and the Crabtree catalyst using simple model compounds as substrates, and was reported to perform exceptionally well.[2]

We now report a more exacting evaluation of the catalyst via the preparation of a number of deuterium and tritium labelled drug candidate molecules. In these studies the labelling was shown to proceed with high regioselectivity and, after a simple filtration step, to afford products with high radiochemical purities directly from the exchange reaction. Moreover, the solid-phase catalyst functioned well with a variety of traditional directing groups including nitro, amide, benzophenone and *N*-heterocycles.[3]

An example of the use of the catalyst for the labelling of a typical drug molecule is given below.



Tolmetin

References

1. Hickey MJ, Jones JR, Kingston LP, Lockley WJS, Mather AN, Wilkinson DJ. *Tetrahedron Lett* 2004; **45**: 8621–8623.

2. Hickey MJ, Jones JR, Kingston LP, Lockley WJS, Mather AN, Wilkinson DJ. Oral presentation at IIS UK symposium Hinxton, UK, 2004. *J Label Compd Radiopharm* 2005; **48**: 523 (Abstract).
3. Hickey MJ, Jones JR, Kingston LP, Lockley WJS, Mather AN, Wilkinson DJ. *J Label Compd Radiopharm*, in preparation.

MEROTERPENOIDS FROM MUSHROOMS, A COLOURFUL GROUP OF NATURAL PRODUCTS

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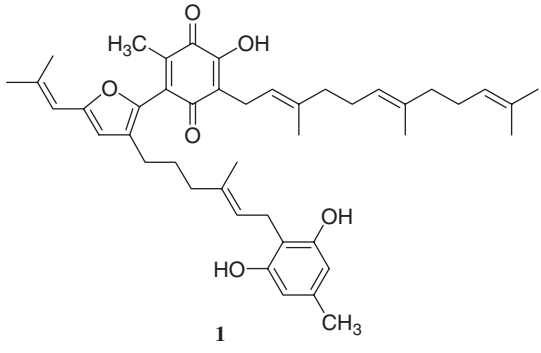
Mushrooms produce a variety of metabolites in which an aromatic nucleus is substituted by a terpenoid chain (meroterpenoids). Some of these compounds have rather unique structures, e.g. the blue albatrellin A (**1**) from *Albatrellus flettii* and the red tridentoquinone (**2**) from *Suillus tridentinus*. **1** was synthesized by coupling of two monomeric co-metabolites, mimicking its possible biosynthesis.



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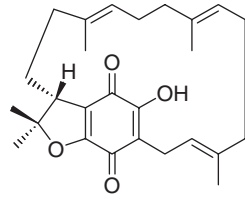

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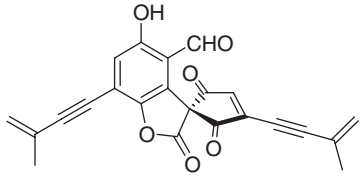
The spirolactonedione ochroleucin A_1 (**3**) is responsible for the red colour reaction exhibited by the yellowish stem base of *Russula ochroleuca* on treatment with aqueous KOH. The compound shows interesting spectroscopic properties and rearranges easily into the more stable dilactone ochroleucin A_2 (**4**). Biosynthetic studies reveal that **3** is formed from two monomeric species by oxidative dimerization.



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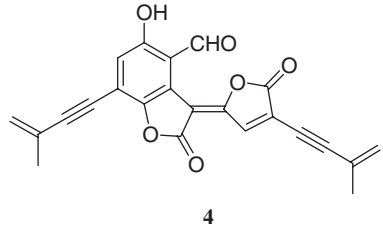

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Some edible boletes produce meroterpenoids, e.g. **2**, originating from 3,4-dihydroxybenzoic acid. The results of recent studies on the biosynthesis of

these compounds by feeding ^{13}C-labelled precursors[1] to young fruit bodies will be presented.[2]

References

1. Lang M, Steglich W. *Synthesis* 2005; 1019.
2. Mühlbauer A, Beyer J, Steglich W. *Tetrahedron Lett* 1998; **39**: 5167.

RADIO- AND STABLE-ISOTOPE LABELLING OF SSR591813 – A NICOTINIC PARTIAL AGONIST

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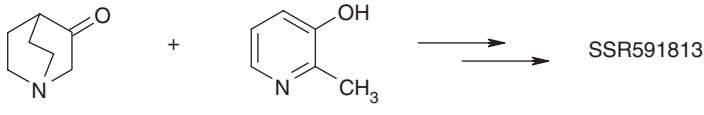
Although the percentage of smokers is tending to decrease in the developed world, the ill-effects of tobacco use remain an important cause of preventable mortality. A variety of therapeutic approaches are becoming available to combat nicotine addiction, and the nicotinic partial agonist SSR591813 is in clinical development as an aid to smoking cessation.[1]

The principal materials used in the synthesis of SSR591813 are 3-quinuclidinone, **1** and 3-hydroxy-2-methylpyridine, **2.**[2]



1 **2**

The presentation describes our investigations towards the labelling of this lead compound with both carbon-14 and stable isotopes, and during which we have developed novel syntheses of 3-hydroxy-2-[^{14}C]methylpyridine, **3** and 3-hydroxy-2-[^{13}C]methyl[1-^{15}N ,2-^{13}C]pyridine, **4**.

3 **4**

References

1. Cohen C, Bergis OE, Galli F, Lochead AW, Jegham S, Biton B, Léonardon J, Avenet P, Sgard F, Besnard F, Graham D, Coste A, Oblin A, Curet O, Voltz C, Gardes A, Caille D, Perrault G, George P, Soubrié P, Scatton B. *J Pharmacol Exp Ther* 2003; **306**: 407.
2. Galli F, Lochead AW, Jegham S, Samson A. PCT International Application 2000: WO 00/53608.

CHIRAL RECOGNITION IN THE ION TRAP MASS SPECTROMETRY USING ISOTOPICALLY LABELLED TRIANGLAMINE MACROCYCLES

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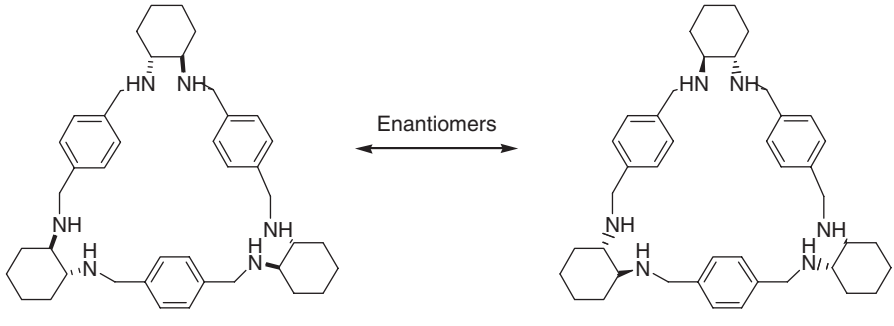
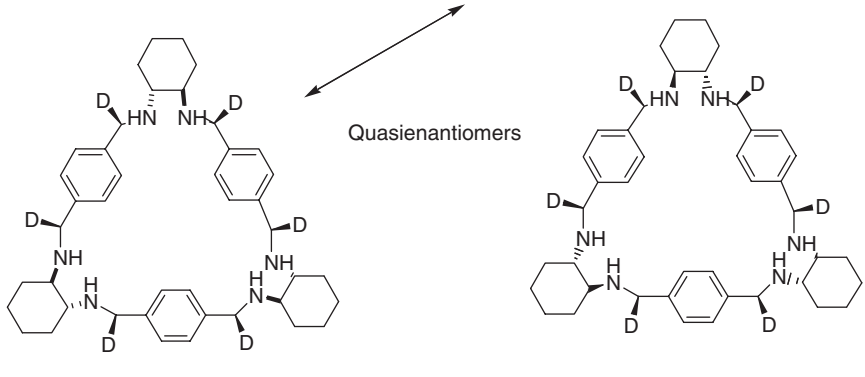
Mass spectrometry is usually considered as a technique that is stereochemically blind and of limited use in the discrimination of enantiomers.

This contribution will report on the synthesis of isotopically labelled macrocycles of the trianglamine type (representative structures are shown below),[1–4] which due to their six deuterium labels are quasienantiomeric.

Furthermore, the use of these novel macrocycles as chiral resolving agents in mass spectrometry for the analysis of enantiomerically pure and enriched compounds and the use of ESI ion trap mass spectrometry as a general tool for chiral analysis will be presented.



(*2R, 3R, 12R, 13R, 22R, 23R*) (*2S, 3S, 12S, 13S, 22S, 23S*)



(*2R, 3R, 12R, 13R, 22R, 23R*) (*2S, 3S, 12S, 13S, 22S, 23S*)

Important instrumental parameters for the chiral discrimination process will be discussed and methods for the evaluation of relative binding energies will be suggested.

References

1. Kuhnert N, Straßnig C, Lopez-Periago A. *Tetrahedron Asymm* 2002; **13**: 123–128.
2. Kuhnert N, Lopez-Periago A, Rossignolo GM. *Org Biomol Chem* 2003; **1**: 1157–1170.
3. Kuhnert N, Patel C, Burzlaff N, Lopez-Periago A. *Org Biomol Chem* 2005; **3**: 1911–1921.
4. Kuhnert N, Lopez-Periago A, Rossignolo GM. *Org Biomol Chem* 2005; **3**: 524–537.

THE APPLICATION OF MICRO REACTORS FOR RADIOCHEMICAL SYNTHESIS

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Current production technology is based on the scale-up of successful laboratory reactions in order to achieve larger scale production. This approach is however fundamentally flawed as at each stage of the process, modifications made to the reactor vessel result in changes to the surface to volume ratio, which in turn have a profound effect on the thermal and mass-transport properties of the reaction. As a result of these variations, it is often necessary to re-optimize the reaction at each stage of the process; consequently the methodology is both costly and time consuming. It is therefore postulated that through the application of micro reaction technology, the transfer of reactions from the laboratory to production will be both rapid and cost effective. The research carried out in Hull and other international centres has now conclusively demonstrated that micro reactors offer many advantages in achieving cleaner, more atom efficient and chemically selective syntheses.[1] These advantages can be attributed to the unique operating conditions associated with micro reactor devices in which the spatial and temporal control of reagents is achieved under a non-turbulent, diffusion limited mixing regime within the reactor channels.

Isotopically labelled molecules are of growing importance within the pharmaceutical and biomedical fields since they may be used within a diverse range of applications. If we consider the present situation within a typical radioisotope group, the first synthesis would be the 'warm' radiosynthesis in which the reaction is spiked with a small amount of radioactivity in order to provide information on overall radioaccountability. Once this trial is successfully completed, a full radiosynthesis ('hot') is undertaken to provide radiolabelled product, which would be repeated as required. The downside of this approach is that the 'warm' reactions can never be considered as truly predictive of the undiluted 'hot' reaction, even if they are carried out on the same chemical scale. Thus, for a radiochemical synthesis the scale out of micro reactors to provide the required quantity would certainly be far less of an issue than that originally perceived within batch reactions. Hence a trial reaction using undiluted radiochemicals could be carried out effectively and safely in a single micro reactor with minimal sample quantity. It is envisaged that once a process has been successfully carried out within a micro reactor (using ng quantities of reagents) and scaled up to the required quantity using a parallel

approach, then this customized system will be retained specifically for this reaction sequence. In this manner the reproducibility of the synthesis is guaranteed and the variability otherwise introduced by the work being carried out by different chemists is removed. In each of the above instances, high yields based on the isotopically labelled starting material are imperative due to relative cost and availability. Ideally, reagents should be used in as close to stoichiometry as possible.

In this presentation various chemical reactions will be used to illustrate the advantages that micro reactors offer for the rapid optimization of reactions, in which the product is typically produced in higher yield and purity. It will be demonstrated that reactions are highly atom efficient and proceed in high yield using stoichiometric quantities of reagents. Furthermore, the use of solid supported reagents adds even greater diversity to the range of reactions that may be performed and enables multi-step reactions to be performed in such a way that analytically pure products may be isolated without additional purification.[2] In addition, specific examples of the synthesis of PET radioligands within a micro reactor will be described, where a range of ^{11}C and ^{18}F-labelled esters have been prepared within a micro reactor in high radiochemical yield.[3]

References

1. Fletcher PDI, Haswell SJ, Pombo-Villar E, Warrington BH, Watts P, Wong SYF, Zhang X. *Tetrahedron* 2002; **58**: 4735–4757.
2. Wiles C, Watts P, Haswell SJ. *Tetrahedron* 2004; **60**: 8421–8427.
3. Lu S, Watts P, Chin FT, Hong J, Musachio JL, Briard E, Pike VW. *Lab Chip* 2004; **4**: 523–525.

PET IN DRUG DISCOVERY AND DEVELOPMENT

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Positron Emission Tomography (PET) and allied non-invasive imaging techniques are being increasingly embraced by the pharmaceutical industry. These imaging modalities allow the assessment of *in vivo* novel drug action at a very early stage of the drug's discovery and development process, enabling earlier decision making about the development potential of novel therapeutics. The *in vivo* characterization of novel molecular targets and disease mechanisms in man is intimately connected with future developments in the diagnosis, management and treatment of human disease. Crucial to the success of this mission is the development of enabling methodologies to support these programmes. Examples of the use of this technique in drug development studies will be presented.

STABLE ISOTOPIC LABELLING OF HETEROCYCLIC COMPOUNDS

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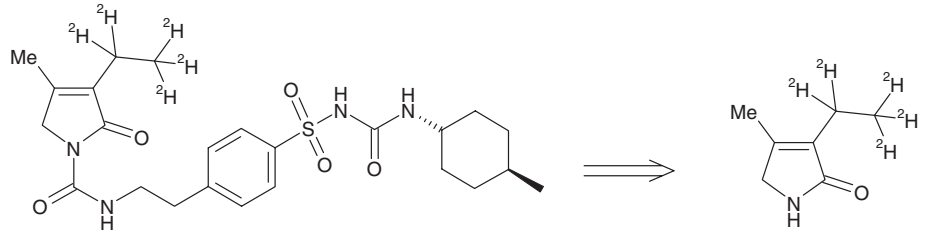
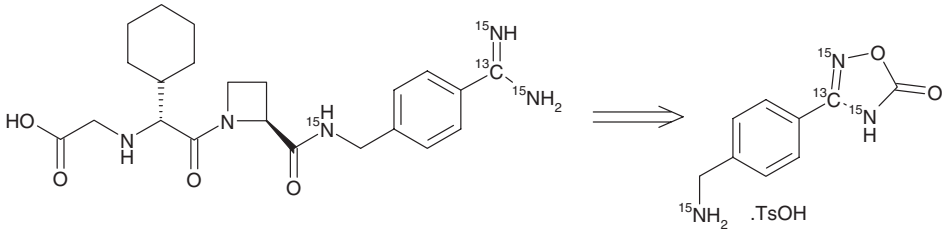


1 SIL-Glimepiride **3**



2 SIL-Melagatran **4**

Syntheses of stable isotopically labelled (SIL) versions of glimepiride **1** (10 steps, 11% overall yield), a blood-glucose-lowering drug, and melagatran **2** (9 steps, 17% overall yield), an anticoagulant with similar uses to warfarin, were synthesized as internal standards for LCMS assays. Modifications of known routes[1,2] to these compounds will be presented as examples of the introduction of stable isotopes into the heterocyclic intermediates **3** and **4**. Factors that influenced the design of such syntheses will be elaborated.

References

1. Weyer R, Hitzel V, Geisen K, Regitz G. US Patent 4379785, Hoechst, 1983.
2. Antonsson KT, Bylund RE, Gustafsson ND, Nilson NOI. PCT International Application WO9429336, Astra AB, 1994.

ABSTRACTS: POSTER PRESENTATIONS

EFFECTIVE SYNTHESIS OF 1β-ACYL GLUCURONIDES BY SELECTIVE ACYLATION

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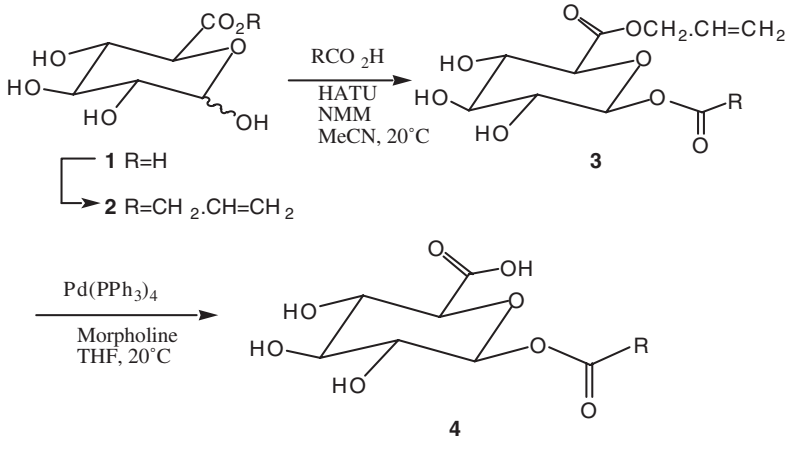
Acyl glucuronides are important metabolites for many carboxylic acid-containing drugs. We report a new method (Scheme) for the chemical synthesis of these molecules by selective 1β-acylation of allyl glucuronate with carboxylic acids, then deprotection through treatment with $Pd(PPh_3)_4$ and morpholine. The method is effective for a range of aryl and alkyl carboxylic acids, including important drugs.



Scheme. Acyl glucuronides via selective acylation

The preparation of allyl glucuronate **2** was significantly improved by using a resin-bound fluoride base, rather than DBU as previously reported. This intermediate was then acylated with a range of carboxylic acids using the

uronium reagent HATU, catalysed by *N*-methyl morpholine, giving the desired 1β-acyl glucuronides **3** in fair to good yield (42–66%) and excellent (at least 95:5) β:α selectivity. Finally deprotection to the free acids **4** was effected using either $Pd(PPh_3)_4$ or a resin-bound Pd equivalent with morpholine, in excellent ($>90\%$) yield. We have synthesized the important acyl glucuronides of ibuprofen, zomepirac, mycophenolic acid and diclofenac together with those for a number of AstraZeneca drug candidates.

ORIGIN OF THE LARGE ISOTOPE-INDUCED SHIFT IN THE ^{1}H-NMR OF *ORTHO*-^{2}H-LABELLED ANILIDES

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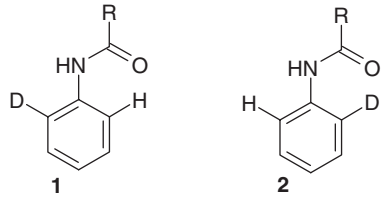
Isotope effects associated with the introduction of deuterium into a molecule are well recognized for both ^{1}H- and ^{13}C-NMR. Generally these effects are both small and additive.[1] However we recently reported an isotopic shift for the remaining *ortho* proton of *ortho*-deuterated anilides.[2] The shift was particularly large, 16 p.p.b. upfield in $CDCl_3$ at 298 K.



It has long been recognized that the deshielding effect of the carbonyl group on the *ortho*-proton in anilides affords a sensitive probe into the conformation about the N–Ar bond. Indeed, unexpected chemical shifts of the *ortho*-proton have been used to investigate the conformations of both mono-*ortho*[2(a)–(c)] and mono-*meta*[2(d)] substituted anilides. We therefore ascribed the origin of the effect to a small preference for conformer 2 over conformer 1.[3] We now report the results of variable temperature NMR studies of one of these systems, *ortho*-deuteroacetanilide, in three solvents. Analysis of the data shows that the position of equilibrium is enthalpy driven and that the effect is electronically rather than sterically mediated. ΔS for the process approximates to zero, whilst ΔH is of the order of -133 J/mol for a non-polar solvent to -53 J/mol for a polar solvent, corresponding to 51.35% and 50.55% respectively of conformer 2 at 298 K. The effect may reflect different dipole-dipole,[4,5] non-bonding-orbital[2(d)] or H-bonding[2(b)] interactions. Though similar effects have previously been advanced as explanations[6] for anomalous isotopic shifts, to our knowledge this is the first direct experimental evidence for an electronically mediated conformational effect arising from a single D-atom substitution.

References

1. Buncel E, Jones JR. *Isotopes in the Physical and Biomedical Sciences*, vol. 2. Elsevier: Amsterdam, 1991; 1–54.
2. (a) Ribera A, Rico M. *Tetrahedron Lett* 1968; 535; (b) Andrews BD, Rae ID, Reichert BE. *Tetrahedron Lett* 1969; 1859–1862; (c) Gribble GW, Bousquet PF. *Tetrahedron* 1971; **27**: 3786; (d) Camilleri P, Kirby AJ, Lewis RJ. *J Chem Soc Chem Commun* 1988; 1537–1538.
3. Lockley WJS, Lewis RJ, Wilkinson DJ, Jones JR. Abstracts of the 14th International Isotope Society (UK group) Symposium, Hinxton 2004. *J Label Compd Radiopharm* 2005; **48**: 515–546.
4. Baweja R. *J Liq Chromatogr* 1986; **9**: 2609–2621; Baweja R. *J Chromatogr* 1986; **369**: 125–131; Baweja R. *Anal Chim Acta* 1987; **192**: 345–348.
5. (a) Filer CN. *J Label Compd Radiopharm* 1999; **42**: 169–197; (b) Lockley WJS. *J Chromatogr* 1989; **483**: 413–418; (c) Lockley WJS. The radiochromatography of labelled compounds. In *Isotopes: Essential Chemistry and Applications II*, Jones JR (ed.). Spec Publ No 68, Royal Society of Chemistry, London 1988; 56–87; (d) El Tayar M, van de Waterbeemd H, Gryllaki M, Testa B, Trager WF. *Int J Pharmacogn* 1984; **19**: 271–281; (e) Turowski M, Yamakawa N, Meller J, Kimata K, Ikegami T, Hosoya K, Tanaka N, Thornton ER. *J Am Chem Soc* 2003; 13836–13849.
6. (a) Novak P, Meic Z, Vikic-Topic D, Sterk H. *J Mol Struct* 1997; **410–411**: 5–7; (b) Novak P, Vikic-Topic D, Gacs-Baitz E, Meic Z. *Magn Res Chem* 1996; **34**: 610; (c) Smrecki V, Vikic-Topic D, Meic Z, Novak P, *Croat Chem Acta* 1996; **69**: 1501; (d) Anet FAL, Basus VG. *J Am Chem Soc* 1980; 3945–3946.

INVESTIGATIONS OF ISOTOPE SCRAMBLING DURING THE DEUTERODECHLORINATION OF *ORTHO*-CHLOROACETANILIDE

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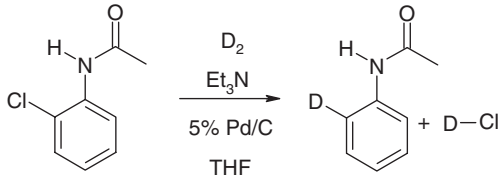
The dehalogenation of haloaromatics is a facile and common approach to labelling organic compounds with hydrogen isotopes. The dehalogenation of chloro-aromatics however, frequently yields low atom% abundance[1] due to isotopic scrambling at the labelling site. Recently the observation of a large deuterium isotopic effect in ortho-deuterated anilides[2] provided a simple method to study this scrambling by ^{1}H-NMR. The model reaction chosen was the deuterodechlorination of *ortho*-chloroacetanilide. Initial screening for maximum isotopic labelling (still only ca. 80%D in the best case) whilst maintaining a deficiency of D_2 gas defined the test reaction: *ortho*-chloroacetanilide (0.5 mmol), 5% palladium on carbon paste (Aldrich 26,670-7, 30 mg) and triethylamine (100 µl) in THF (2 ml) with D_2 (0.36 mmol) at ambient temperature and pressure.



The studies failed to identify all the processes involved in the scrambling reaction, though some useful conclusions could be drawn. *N*-Deuteration of the substrate showed that the scrambling probably did not arise from the amide NH. Addition of D_2O to the system showed only a small increase in %D, but addition of H_2O showed no obvious decrease. Addition of drying agents or use of new dried solvent had no effect. ^{2}H-NMR studies, using excess D_2, showed the formation of exchangeable[3] deuteron signals with time (ND and HOD only, there was no detectable labelling of the solvent or triethylamine[†]) but the rate was slow compared with the dehalogenation reaction and was unrelated to the %D of the *o*-deuteroacetanilide product.

[†]The authors would like to thank Dr Cor Janssen for the opportunity to analyse similar reactions carried out with tritium via ^{3}H-NMR. These studies confirmed that tritiated water was formed in all the solvents studied (including THF) whilst the solvents remained unlabelled.

This was essentially constant from the earliest sampling point (18% reaction) to the end of the dehalogenation reaction at ca. 5 h. However, very significant decreases in %D were observed when a delay of 7 or 18 h was introduced before the addition of the substrate, or if the rate of the dehalogenation was slowed by addition of iodobenzene (a catalyst poison for dehalogenation). In these cases the competing H_2O/D_2 isotope equilibration could well have been the dominant process leading to the very low %D achieved. Given the known[3(b)] fractionation of H_2 isotopomers on Pd it is possible that even minor H/D exchange processes could lead to an over-representation of the key (i.e. reactive) HD or H_2 on the catalyst and hence to scrambling in the product.

Studies are continuing, however, in view of our results it would seem advisable to: (1) avoid methanol as solvent and (2) to ensure that the rate of any target dechlorination reaction is maximized before finally resorting to the labelling step.

References

1. Wilkinson DJ, Hickey MJ, Kingston LP, Mather AN. *Synthesis and Applications of Isotopically Labelled Compounds, Proceedings of the 8th International Symposium*, Boston, USA, 2003, vol. 8, Dean DC, Filer CN, McCarthy K (eds). Wiley: Chichester, UK, 2004; 47–50.
2. Lockley WJS, Lewis RJ, Wilkinson DJ, Jones JR. Abstracts of the 14th International Isotope Society (UK group) Symposium, Hinxton 2004. *J Label Compd Radiopharm* 2005; **48**: 515–546.
3. (a) Sajiki H, Kurita T, Esaki H, Aoki F, Maegawa T, Hirota K. *Org Lett* 2004; **6**: 3521–3523; (b) Sidorov G, Susan A, Myasoedov NF. *Synthesis and Applications of Isotopically Labelled Compounds, Proceedings of the 7th International Symposium*, Dresden, Germany, 2000, vol. 7, Pleiss U, Voges R (eds). Wiley: Chichester, UK, 2001; 109–113.

A NOVEL SYNTHESIS OF [$^2H_6$]2-METHYL-3-BUTYN-2-OL

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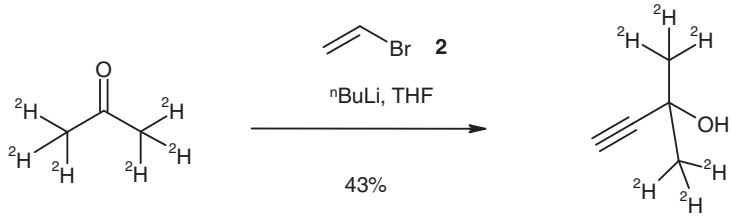

1 3

[$^2H_6$]-Labelled 2-methyl-3-butyn-2-ol **3,** synthesized from readily available hexadeuteroacetone **1** by a known route,[1] had been used to prepare a labelled target for use as a mass spectrometric standard in drug development. When the first product coupled from **3** was analysed, it was found to be unacceptable for further use, since it showed $\sim$0.5% of the unlabelled molecular ion in the mass spectrum. The source of the unlabelled contamination was traced to the acetylenic reagent used to synthesize **3**. Literature evidence suggests that the probable reason behind this lies in the use of solvent acetone to enable the packing of higher volumes of acetylene in commercial gas cylinders.[2]

Alternative methods of preparing **3**, that would avoid the use of commercial acetylene gas, were considered. The resulting novel synthesis of **1** was as simple and practical as the previous one,[1] exemplifying the little known dehydrobromination of vinyl bromide as a source of lithium acetylide.[3]

Mass spectral analysis of **3** itself does not enable detection of unlabelled contamination. A rapid derivatisation method, based on the known Mannich reaction of acetylenes with secondary amines,[4] was developed to solve this problem.

References

1. Stanjek V, Miksch M, Boland W. *Tetrahedron* 1997; **53**: 17699–17710.
2. Armarego WLF, Perrin DD. *Purification of Organic Chemicals* (4th edn). Butterworth-Heinemann: Oxford, 1996; 71.
3. (a) Neumann H, Seebach D. *Tetrahedron Lett* 1976; **17**: 4839–4842; (b) Gilman H, Haubein AH. *J Am Chem Soc* 1945; **67**: 1420–1421; (c) Midland MM. *J Org Chem* 1975; **40**: 2250–2252.
4. Beiber LW, Da Silva MF. *Tetrahedron Lett* 2004; **45**: 8281–8283.

IMPROVED ANALYSIS OF TRITIATED SAMPLES VIA A ^{3}H-NMR CRYOPROBE

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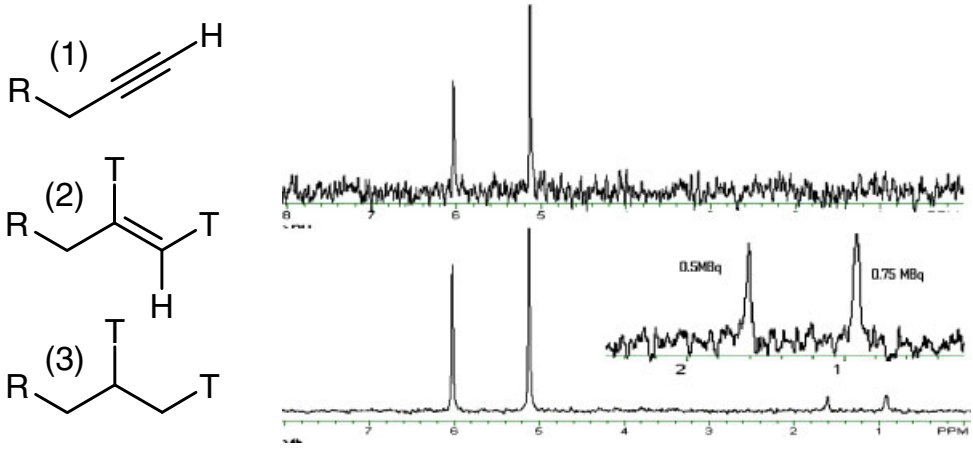
Tritium Nuclear Magnetic Resonance Spectroscopy (^{3}H-NMR) is the method of choice for the analysis of ^{3}H-labelled compounds. However, even at the highest magnetic fields currently practicable the energy differences between nuclear spin levels are small and the NMR signals correspondingly weak. The output from the instrument can be amplified by any required factor, but the 'detectability' of the signal depends on the signal-to-noise ratio, which is, essentially, limited by the electrical noise in the detector coil and first amplifier stage, where the signal is still very small. One solution to this problem is to reduce the noise in the detector coils and amplifier by cooling to very low temperatures using a cryo-probe.

At the University of Surrey we have been evaluating a high field (533 MHz) ^{3}H-instrument equipped with a cryo-probe of this type.[1] The figure below shows one example: the ^{3}H-NMR spectrum of the product from a partial deuterium tritide (DT) reduction of a terminal alkyne **1** recorded using a conventional probe and a cryo-probe over 32.5 K scans. The major resonances arise from the *cis*-addition of deuterium tritide as expected (with some isotopic exchange but without any obvious isomerization) to yield the terminal alkene **2**. Use of the cryo-probe enabled us to continue searching for isomerization at lower levels. None was seen, but with the new sensitivity the small amount of over reduction to yield the [^{3}H]propyl product **3** became observable. Similar improvements are reported for the analyses of a further six DT reductions of various unsaturated systems.



The overall improvement in sensitivity (calculated from all the resonances in six independent ^{3}H-spectra) was 4.3 ($\pm$ 1.1) fold. In absolute terms the small (^{3}H-propyl) resonances in the above figure represent 0.5 and 0.75 MBq (20 and 14 μCi) of ^{3}H-activity.

Reference

1. Bloxsidge JP, Garman RN, Gillies DG, Jones JR, Lu SY. *Synthesis and Applications of Isotopically Labelled Compounds, Proceedings of the 8th International Symposium*, Boston, USA, 2003, vol. 8, Dean DC, Filer CN, McCarthy KE (eds). Wiley: Chichester, 2004; 381–384.

SOME INVESTIGATIONS OF THE EXCHANGE-LABELLING OF ALLYL TERMINAL METHYLENE GROUPS OVER PALLADIUM CATALYSTS

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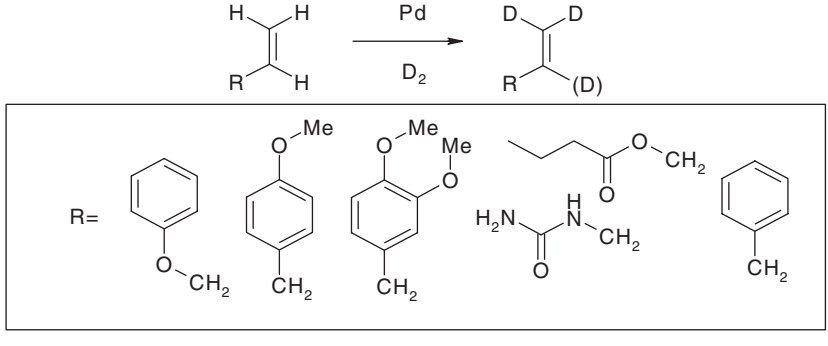
The isotopic exchange labelling of the terminal methylene groups of allyl and related systems with deuterium and tritium has been documented previously.[1] Often such labelling is merely a transitional step during the complete reduction of these systems. In such cases the resulting labelled hydrocarbon moiety bears an excess (sometimes very large) of isotope in the terminal methyl group.[2] As part of a more general series of investigations of the exchange processes accompanying alkene hydrogenations[†] we have recently investigated this terminal exchange process in some detail using D_2, or in one case DT.



All the substrates readily underwent the isotopic exchange process. In addition, for those substrates in which the appropriate resonances were resolved, analysis of the exchanged product showed an equal amount of deuterium in both of the terminal *cis* and *trans* positions. It therefore seems likely that the exchange process itself proceeds via one or more symmetrical intermediates.

The results presented also suggest that the exchange of terminal methylene groups in allyl systems, using a deficit of isotopic hydrogen, could provide a viable route to the terminal hydrogen isotope labelling of such systems, provide the appropriate separation systems are available.

[†]The authors would like to acknowledge the scientific and financial support (to EA) provided by Johnson Matthey and the other contributors to the ATHENA consortium during the course of these studies.

References

1. (a) Elvidge JA, Jones JR, Lenk RM, Tang YS, Evans EA, Guildford GL, Warrell DC. *J Chem Res (S)* 1982; 82; (b) Guildford GL, Evans EA, Warrell DC, Jones JR, Elvidge JA, Lenk RM, Tang YS. *Synthesis and Applications of Isotopically Labelled Compounds, Proceedings of the 1st International Symposium*, Kansas City, USA, 1982, Duncan WP, Susan AB (eds). Elsevier: Amsterdam, 1983; 327–330.
2. (a) Tang YS, Morimoto H, Un S, Rapoport H. *Synthesis and Applications of Isotopically Labelled Compounds, Proceedings of the 2nd International Symposium*, Kansas City, USA, 1985, Muccino RR (ed.). Elsevier: Amsterdam, 1986; 497–500; (b) Wilkinson DJ, Lockley WJS. *J Label Compd Radiopharm* 1985; **22**: 883–892; (c) Voges R, Wartburg BR, Loosli HR. *Synthesis and Applications of Isotopically Labelled Compounds, Proceedings of the 2nd International Symposium*, Kansas City, USA, 1985, Muccino RR (ed.). Elsevier: Amsterdam, 1986; 371–376; (d) Kingston LP, Lockley WJS, Mather AN, Wilkinson DJ. *Synthesis and Applications of Isotopically Labelled Compounds, Proceedings of the 5th International Symposium*, Strasbourg, France, 1994, Allen J, Voges R (eds). Wiley: Chichester UK, 1995; 57–60.

ENANTIOSELECTIVE SYNTHESIS OF ISOTOPICALLY LABELLED AMINO ACIDS AND NITROGEN HETEROCYCLES

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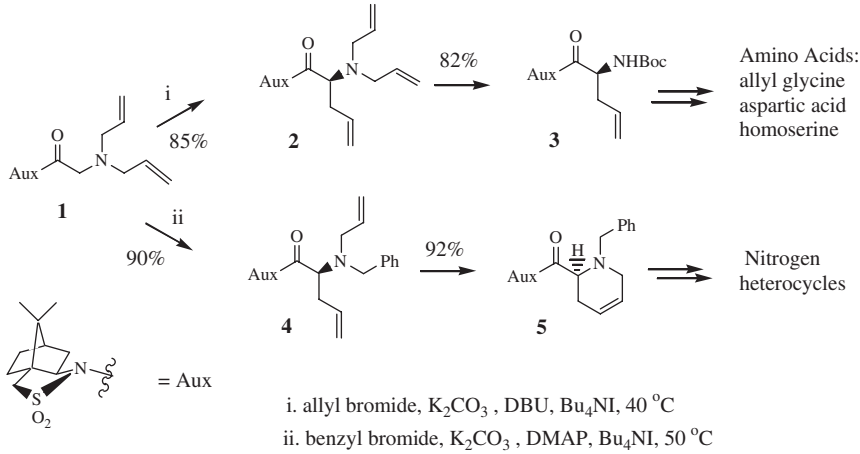
The [2,3]-Stevens rearrangement of ammonium ylides is a useful carbon–carbon bond forming reaction in synthesis.[1] Recently, Coldham *et al*. used this rearrangement to prepare racemic allyl glycine.[2] This methodology has been developed for the enantioselective synthesis of amino acids and nitrogen heterocycles using Oppolzer's sultam as the chiral auxiliary.

Two key intermediates **2** and **4** were prepared in high yield and with good stereocontrol (>95% de). Ring closing metathesis of **4** gave the unsaturated nitrogen heterocycle **5**.



Starting from isotopically labelled glycine or α-bromoacetate, this chemistry can be used to prepare labelled L and D-amino acids including allyl glycine, aspartic acid and homoserine. For example, L-[1,2-$^{13}C_2$,^{15}N]homoserine has been prepared from [$^{13}C_2$,^{15}N]glycine for use in biosynthetic studies.

References

1. Stevens TS. *J Chem Soc* 1928; 3193–3197.
2. Arbore APA, Cane-Honeysett DJ, Coldham I, Middleton ML. *Synlett* 2000; **2**: 236–238.

BISCHLER-NAPIERALSKI-PSCHORR SYNTHESIS OF (*R*)-(-)-[6a-^{14}C]APOMORPHINE

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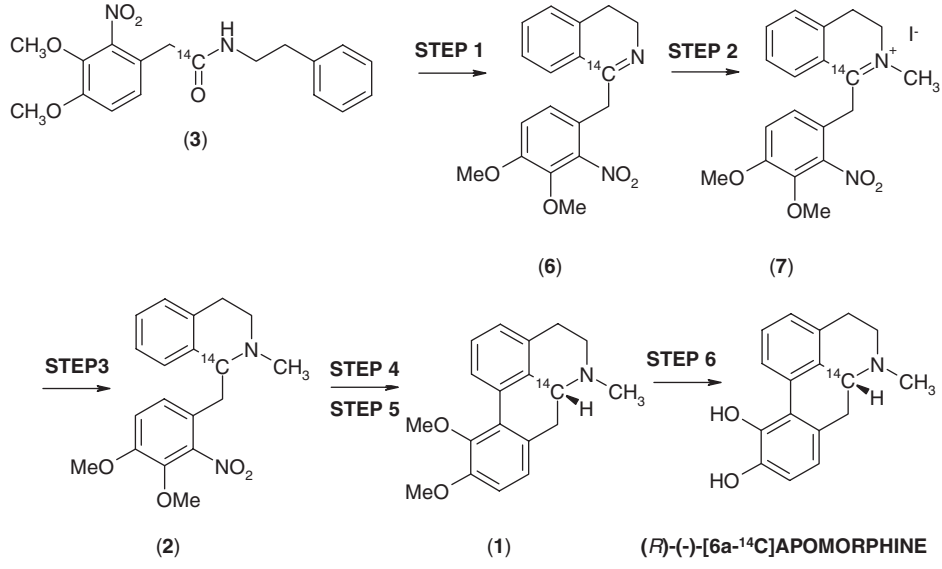
Synthetic methodology

A strategy for the incorporation of a single carbon-14 label has been developed in our laboratories to give (*R*)-(-)-[6a-^{14}C]apomorphine, and is shown below.



Step 1. Bischler-Napieralski cyclodehydration reaction to 1-(3,4-dimethoxy-2-nitrobenzyl)dihydro[1-^{14}C]isoquinoline **6**.

Step 2. Quaternization at the isoquinoline nitrogen with iodomethane to give the isolated product 1-(3,4-dimethoxy-2-nitrobenzyl)dihydro[1-^{14}C] isoquinoline methiodide **7**.

Step 3. Reduction of [^{14}C]compound **7** with ethanolic sodium borohydride to afford 1-(3,4-dimethoxy-2-nitrobenzyl)-2-methyltetrahydro[1-^{14}C] isoquinoline **2**.

Step 4. Reductive Pschorr cyclization to (*R*/*S*)-($\pm$)-[6a-^{14}C]apomorphine dimethyl ether.

Step 5. Chiral separation of the (*R*/*S*)-($\pm$)-enantiomers.

Step 6. The selective *O*-demethylation of the (*R*)-(-)-enantiomer **1** to give the non-selective D_1/D_2 dopamine receptor agonist:

(*R*)-(-)-[6a-^{14}C]Apomorphine had a radiochemical purity of $\geqslant 98\%$, with a chiral purity of $\geqslant 99\%$ and a specific activity of 55 mCi/mmol.

IODONIUM CHEMISTRY: SCOPE AND SELECTIVITY IN AROMATIC NUCLEOPHILIC LABELLING REACTIONS

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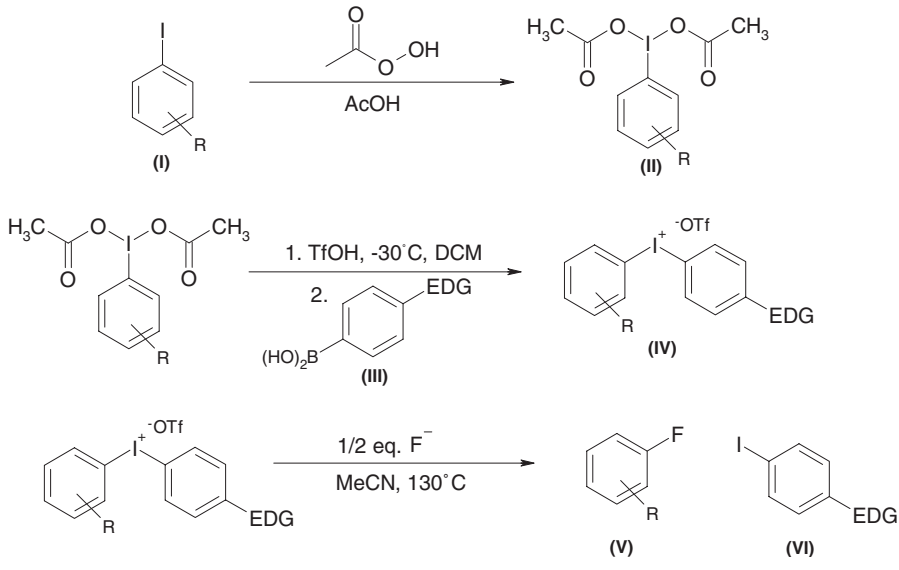
The success of PET is based on the ability of chemists to incorporate positron emitting isotopes into molecules of interest. However, the PET radiochemist still faces quite a number of challenges. One such challenge is the introduction of fluorine-18 onto an electron rich aromatic ring. If we focus on so-called high specific activity chemistry, fluorine-18 has typically been incorporated onto aromatic rings with reasonable amounts of success on the position *para* to the electron withdrawing group (EWG).

This reaction also works on the position *ortho* to the EWG but yields tend to be lower (1–5% radiochemical yield). However, for aromatic ring systems in which the EWG is substituted by an electron donating group (EDG) or where the reaction is attempted on the *meta* position, the synthesis does not normally produce sufficient amounts of radiolabelled product for *in vivo* studies. As many new drug substances do have a fluorine attached to an electron rich aromatic ring or in the meta position, a strategy towards labelling these compounds is highly desirable. It has been demonstrated that the use of iodonium salts has the potential to greatly increase the yields in systems or positions that are normally not reactive enough to give sufficient yields. The idea behind the iodonium chemistry is that nucleophilic attack occurs on the more electron deficient ring. As a result, good counter rings need to contain an electron donating group(s). Unfortunately, little has been reported on the use of appropriate counter rings, the influence of various side chains, solvent systems, temperature, steric hindrance, varying sidegroups, electron density, etc. and the general scope of the reaction. Here we present a methodological approach towards characterizing the reactivity and selectivity of iodonium chemistry as a means for introducing, e.g. fluoride or cyanide onto deactivated aromatic ring systems.



Typically, the aryliodonium salt was prepared by reacting an aryl boronic acid (III) with the appropriate diacetoxyiodobenzene (II). Interestingly, in numerous cases it was possible to react the diacetoxybenzene directly with anisole, leading to improved yields and/or much reduced purification steps. Subsequently, the iodonium salt was reacted with CsF or KF and the ratios of desired products vs undesired products determined through HPLC. The following variables were investigated: solvent, temperature (conventional vs microwave), phase transfer agent, side chain on target ring, and electron donating group on the counter ring.

The results for the fluorination reaction varied quite extensively. Our work will assist in choosing the reaction conditions that are most likely to yield the desired product. The ability to react the diacetoxybenzene directly with anisole has greatly facilitated the production of iodonium salts. Further work is ongoing to investigate the use of, e.g. veratrole as the electron rich aromatic ring and the use of cyanide as nucleophile. We will shortly investigate if the cold chemistry is a good predictor for radiochemical yields.

IMPROVED RADIOSYNTHESIS OF [^{11}C]DAA1106 AND PRELIMINARY *IN VIVO* EVALUATION IN A RAT BRAIN BY MICROPET IMAGING

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[^{11}C]DAA1106 **1** has been shown to be a promising PET radioligand for peripheral benzodiazepine receptors (PBR) [1]. For evaluation studies using a microPET scanner our initial objective was to implement robust high yielding productions of **1** at high specific radioactivities. We found the method outlined by Zhang *et al.* [1] consisting of methylation of the desmethyl precursor **2** with [^{11}C]iodomethane in the presence of NaH to be low yielding (ca. 10%). Therefore, for our regular productions we have now developed two higher yielding methods.

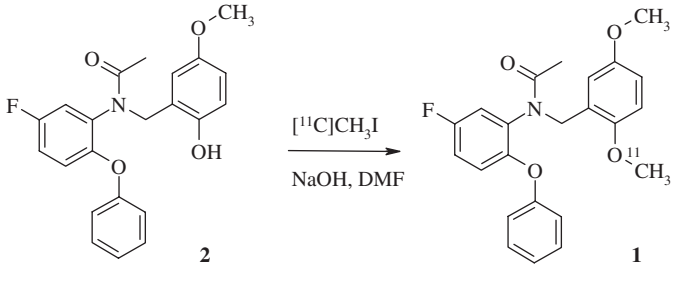

Figure 1.

Method A: To 1 mg of **2** in DMF (300 µl) and 10 M NaOH (10 µl) was added [^{11}C]MeI at RT then stirred for 3 min (Figure 1). **1** was obtained in 80% ($n = 3$) radiochemical yield (RCY).

Method B: To a solution of **2** (1 mg) in DMF (100 µl) loaded unto a HPLC injector loop was passed [^{11}C]MeI at RT. **1** was obtained in 75% ($n = 5$) RCY.

Both methods were implemented on automated systems yielding 2.6 GBq (method A), 6.3 GBq (method B) both at high purities (>98%) and good specific radioactivity of 225 GBq/µmol.

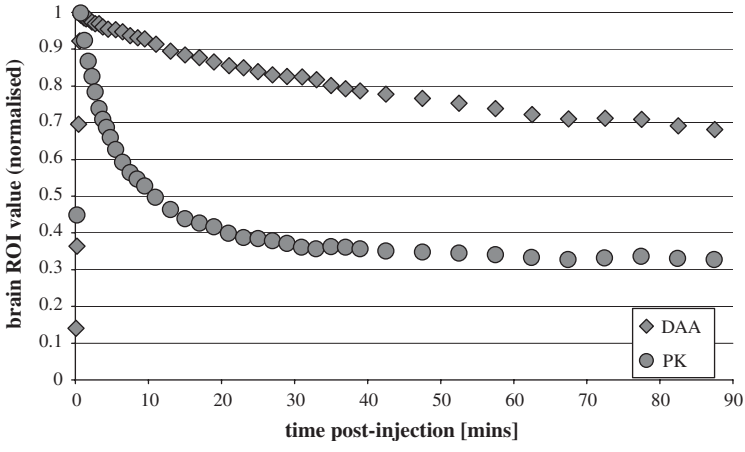

Figure 2.

For a preliminary evaluation of [^{11}C]DAA1106 a microPET study was then performed on a SHR rat to compare it's brain kinetics with the widely used PBR radioligand [^{11}C]PK11195. Time-activity curves (Figure 2) shows a rapid uptake of **1** similar to [^{11}C]PK11195 however, with a significantly slower elimination. Further microPET evaluations are now planned.

Reference

1. Zhang MR *et al. Nucl Med Bio* 2003; **30**: 513–519.

ISOTOPIC LABELLING WITHIN MICRO REACTORS

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Within pharmaceutical and medicinal research there is a need for the fast, efficient, clean and cost effective synthesis of isotopically labelled molecules. Micro reactors, with their unique spatial and temporal features, offer a unique solution to making these ideals a reality.[1]

Photolithographically fabricated borosilicate glass micro reactors have been used for the current work (Figure 1). The small dimensions of the channels within the reactor (typically $<200\,\mu m$) allow for rapid diffusion between laminar flowing streams of reagents which reduce conventional mixing times, seen with lab and plant scale equipment, to give quantitative yields. The net result is a high throughput process which may be scaled out to meet client demands, whilst retaining the original high yielding synthetic methodology.

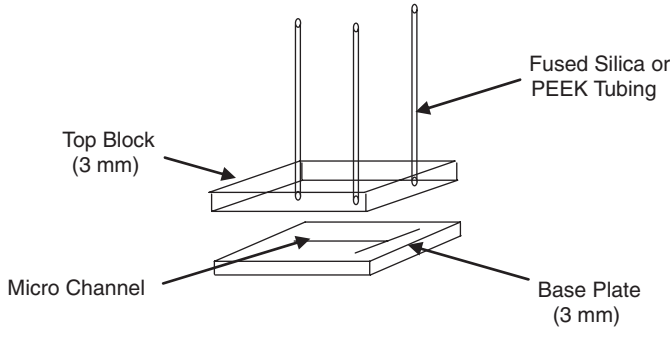
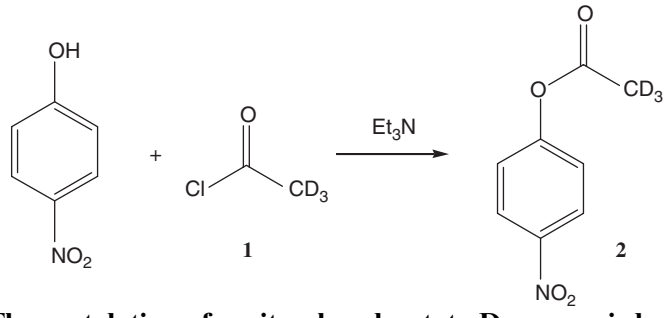


Figure 1. A 'T' shaped micro reactor as used for the described reaction

Esters are functional groups of synthetic importance for many reasons,[2] and as such have been chosen as a model study for the research project. Initially, *p*-nitrophenylacetate-D3 **2** has been successfully synthesized in excellent yields ($>99\%$) within a two step, series arrangement of hydrodynamically driven micro reactors using deuterated acetyl chloride **1** (Scheme 1).

The methodology to be presented demonstrates the atom efficiency achieved using the setup. Consideration will also be given to the future synthesis of a library of analogues and on-line purification of by-products, further decreasing the overall process time (Scheme 1).



Scheme 1. The acetylation of *p*-nitrophenylacetate-D_3 as carried out within the described micro reactor setup

References

1. Fletcher PDI, Haswell SJ, Pombo-Villar E, Warrington BH, Watts P, Wong SYF, Zhang X. *Tetrahedron* 2002; **58**: 4735.
2. Otera J. '*Esterification*': *Methods, Reactions and Applications*, Wiley: Chichester, 2003.

THE USE OF SOLID-SUPPORTED REAGENTS IN CONTINUOUS FLOW REACTORS

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Under increasing environmental and financial pressure, the chemical industry as a whole have begun to explore many routes in order to improve both the cleanliness and efficiency of synthetic processes. One such approach is the application of micro reaction technology, which enables reactions to be performed more rapidly, efficiently and selectively than traditional batch scale reactions.[1] Although many groups have demonstrated the application of micro reaction technology to the synthesis of small organic molecules, few have addressed the problems associated with the purification of products synthesized in continuous flow systems.[2] With this in mind, we investigated the incorporation of solid-supported catalysts into micro fabricated reactors in order to synthesize analytically pure compounds. The work described herein demonstrates the incorporation of two supported reagents into a micro fabricated device (Figure 1) for the multi-step synthesis of an α,β-unsaturated compound 1 (Scheme 1).

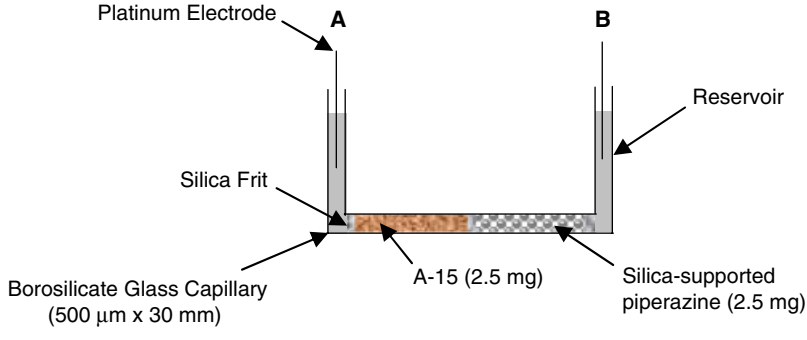
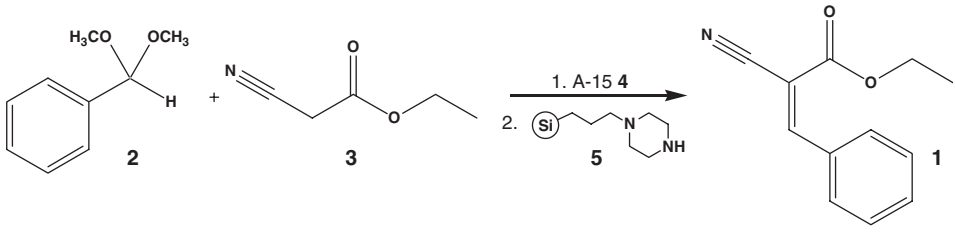


Figure 1. Schematic illustrating the reactor used for the multi-step synthesis of α,β-unsaturated compounds by EOF

Using the set-up illustrated in Figure 1, a solution of dimethoxymethyl benzene **2** and ethyl cyanoacetate **3** (1.0 M in MeCN) were placed in reservoir A and MeCN in reservoir B. The reagents were mobilized through the packed bed using electroosmotic flow and the reaction products collected in reservoir B after 20 min. The reaction products were subsequently analysed by GC–MS



Scheme 1. Illustration of the multi-step synthesis performed in the micro fabricated device using a polymer supported acid catalyst 4 and a silica supported organic base 5

whereby the conversion of acetal **2** to product **1** was determined [99.99%, $\%\mathrm{RSD} = 3.0 \times 10^{-3}$ ($n = 15$)]. Once successfully optimized, the device was operated for 2.5 h whereby product **1** was obtained as a white crystalline solid (0.015 g, 99.4%). Analysis of the 'crude' product by NMR spectroscopy confirmed excellent product purity.

In summary, we have demonstrated that the incorporation of supported catalysts within micro fabricated reactors enables the continuous flow synthesis of analytically pure compounds without the need for additional product purification. Consequently, we believe that the methodology described herein is suitable for the synthesis of isotopically labelled compounds.

References

1. Wiles C, Watts P, Haswell SJ. *Tetrahedron* 2004; **60**: 8421.
2. Brody J, Yager P. *Sens Act A* 1997; **58**: 13.

