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ABSTRACTS OF THE 17TH INTERNATIONAL ISOTOPE SOCIETY (UK GROUP) SYMPOSIUM SYNTHESIS AND APPLICATIONS OF LABELLED COMPOUNDS 2008

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Meeting summary

The 17th annual symposium of the International Isotope Society's United Kingdom Group took place at the Wellcome Genome Campus, Hinxton, Cambridge, UK on 9th October 2008. The meeting was attended by around 100 delegates from academia, the life sciences and fine chemical companies.

Delegates were welcomed by Dr Ken Lawrie (GlaxoSmithKline, UK, chair of the IIS (UK group). 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 an afternoon session chaired by Prof Chris Willis (University of Bristol, UK) and Dr Nigel Botting (University of St Andrews, UK) respectively. The meeting concluded with remarks from Dr Ken Lawrie (GlaxoSmithKline, Stevenage, UK).

This year's symposium had a good attendance from students. Moreover, an excellent level of sponsorship was achieved, and the symposium proved self-financing. The meeting venue again proved very popular. The next UK symposium is provisionally planned for 12th November 2009.

Meeting programme

9:00 am Registration/Morning Coffee/Poster Viewing/Manufacturers Exhibition

9:50 am Welcome: Dr. Ken Lawrie [GlaxoSmithKline, Stevenage, UK]

Morning Session: Chair:- Prof. Chris Willis [University of Bristol, UK]

10:00 am Prof. Jonathan Williams [University of Bath, UK]
''Alcohols as alkylating agents for C-C and C-N bond formation''

10:30 am Prof. Guy Lloyd-Jones [University of Bristol, UK]
''Aryl-O to aryl-S rearrangements: Isotopic labelling, mechanism, side-reactions and application''

11:00 pm Posters Viewing/Manufacturers Exhibition/Coffee & Tea

11:25 am Dr. Stephanie Irvine [University of Strathclyde, UK]
''Highly active iridium(I) complexes for catalytic hydrogen isotope exchange and selective hydrogenation''

11:55 am Dr. Ingid Dijkgraaf, [Technical University, Munich, Germany]
''Radiolabelled peptides: Imaging tumor metastasis with PET''

12:15 pm Dr. Maarten Vliegen [Johnson & Johnson, Belgium]
''Tritium labelling of a new tuberculosis drug, an undesired isotope effect and an alternative solution via ICP-MS''

12:35 pm Posters Viewing/Manufacturers Exhibition/Buffet Lunch

Afternoon Session: Chair:- Dr. Nigel Botting [University of St Andrews, UK]

2:10 pm Dr. Steve Pleasance [Quotient Bioresearch, UK]
''The application of isotope labelling within Quotient Bioscience''

2:40 pm Dr. Cyrille Landreau [Selcia, Ongar, UK]
''Total synthesis of ^{14}C-labelled procyanidin B2''

3:00 pm Poster Viewing/Manufacturers Exhibits/Coffee & Tea

3:30 pm Dr. Stefan Raddatz [sanofi-aventis, Germany]
''Strategies for ^{3}H-labelling of decapeptide HOE140''

3:50 pm Dr. Paul Allen [AstraZeneca Charnwood, Loughborough, UK]
''Metallation of heteroaryls and its application to isotopic labelling''

4:10 pm Dr. Hazel Weldon [GE Healthcare, Cardiff, UK]
''The synthesis of singly-labelled [^{14}C]aromatic rings''

4:30 pm Concluding Remarks. Dr Ken Lawrie [GlaxoSmithKline, Stevenage, UK]

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ORAL PRESENTATION ABSTRACTS

ALCOHOLS AS ALKYLATING AGENTS FOR C-C AND C-N BOND FORMATION

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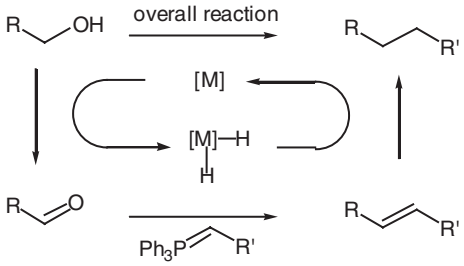
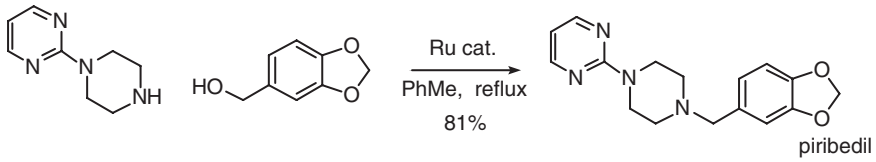
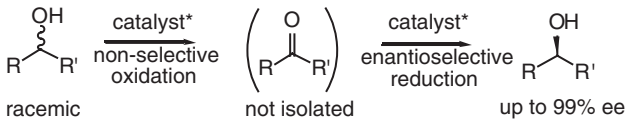
We have recently developed an indirect Wittig reaction which can be employed to construct C-C bonds from alcohols. The reaction is made possible by the ability of transfer hydrogenation catalysts to borrow hydrogen from the substrate alcohol and return it to the product alkene. Ruthenium carbene complexes have been especially effective for this reaction, and the reaction tolerates a range of alcohols and phosphonium ylides.[1]



A related strategy has been used in the conversion of alcohols into amines via intermediate aldehydes and imines. The amination reaction is successful for the construction of secondary and tertiary amines, including the drug molecule Piribedil.[2]



We are currently exploring the borrowing hydrogen strategy for the deracemisation of alcohols, where oxidation of a racemic alcohol provides an achiral ketone which is then reduced back to the alcohol with enantioselectivity.[3]



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ARYL-*O* TO ARYL-*S* REARRANGEMENTS: ISOTOPIC LABELLING, MECHANISM, SIDE-REACTIONS AND APPLICATION

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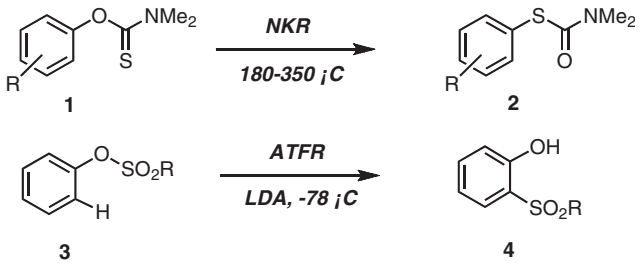
The organic chemistry of sulfur is a vast field, forming a major branch of modern organic chemistry that is undergoing continual development and expansion. The aryl-sulfur linkage, Ar-S, at its manifold oxidation levels is encountered frequently in pharmaceutical motifs, and comprises an important element of organosulfur chemistry. There are numerous methods for the preparation of Ar-S species each with its own benefits and problems. Phenols are attractive precursors as many are readily available or readily prepared. We have been exploring the mechanism of two Ar-S generating reactions. The first is quite well established (**1** → **2**) first reported in 1965,[1] and known as the Newman-Kwart rearrangement,[2] whilst the second (**3** → **4**) is much more recent and is referred to as the anionic thia-Fries rearrangement[3]



The presentation will show how isotopic labelling has proven essential in the elucidation of the mechanisms of these processes[4] and their accompanying side-reactions.[5] This mechanistic investigation has facilitated the development of new and improved conditions for these reactions which have useful applications.[6]

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HIGHLY ACTIVE IRIDIUM(I) COMPLEXES FOR CATALYTIC HYDROGEN ISOTOPE EXCHANGE AND SELECTIVE HYDROGENATION

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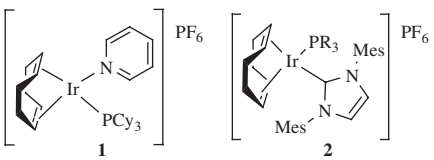
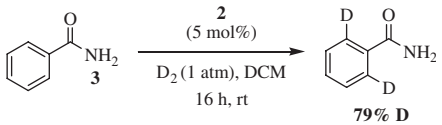
Hydrogen Isotope Exchange

Hydrogen isotope exchange (HIE) represents an effective way of following the metabolic pathways of potential drug candidates and, therefore, is of increasing importance to the pharmaceutical industry.



The ideal situation would be to utilise catalytic quantities of a transition metal species to carry out this transformation on a fully functionalised compound. A limited range of iridium catalysts has been developed and applied to this process with varying success. Traditionally, the most effective catalyst used in this field is Crabtree's catalyst **1**.[1] However, often super-stoichiometric amounts of this species and long reaction times are required, with low levels of labelling being encountered. With this in mind, a series of novel iridium(I) complexes of type **2**, bearing specifically bulky *N*-heterocyclic carbene ligands together with bulky phosphine ligands, have been developed and applied to HIE.[2] At only **5** mol% complex loading, high incorporation is achieved into substrate **3** (**Scheme 1**). Furthermore, the site of labelling is highly predictable and reproducible. Substrate **3** is a traditionally difficult substrate to label and, indeed, *110 mol% of Crabtree's catalyst* is required to achieve a mere 65% labelling.[3] **Scheme 2** shows another impressive result, with substrate **4** being labelled to an extremely high degree. Again, a *stoichiometric amount of Crabtree's catalyst* was previously required to induce a similar level of labelling. Finally, after conducting loading and time studies on substrate **5**, it was found that only 0.5 mol% of the catalyst was required to deliver an extremely high level of labelling over a remarkably short reaction time (**Scheme 3**).



Scheme 1.

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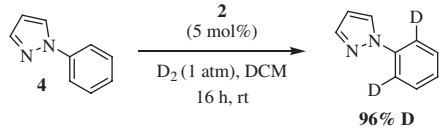
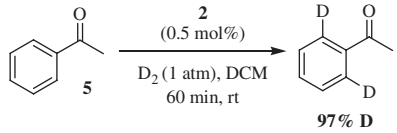


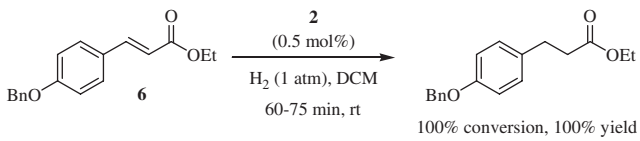
Scheme 2.



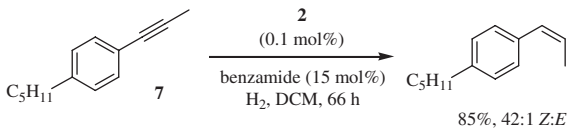
Scheme 3.

Selective Hydrogenation

Based on the outstanding levels of activity shown in C-H activation, we felt that these same iridium-based species had the potential to act as selective hydrogenation catalysts. To investigate this hypothesis, we chose substrate **6**, containing a benzyl group, which is easily removed under hydrogenation conditions. As shown in **Scheme 4**, using only 0.5 mol% of the complex, substrate **6** was fully reduced in extremely short order, and we were pleased to observe that the benzyl group stayed intact throughout the reaction. Under the same conditions with *Crabtree's catalyst, only a 28% conversion to product was obtained after 1 hour*. Alongside this, we have investigated whether our complexes could be used for the semi-hydrogenation of alkynes, i.e. reducing an alkyne to an alkene. With only 0.1 mol% of complex **2**, and employing benzamide as a poison, the alkyne, **7**, can be selectively reduced, yielding 85% of the corresponding alkene with a *Z*:*E* ratio of 42:1 (**Scheme 5**).



Scheme 4.



Scheme 5.

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RADIOLABELED PEPTIDES: IMAGING TUMOR METASTASIS WITH PET

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The chemokine receptor CXCR4 plays an important role during metastasis and has been found to be responsible for tissue specific homing of circulating tumor cells, directing metastases to liver, lung and bone marrow (mammary cancer, prostate cancer etc.). So far, CXCR4 has been found to be overexpressed in more than 30 different types of cancer. The aim of this ongoing study is the development of probes for *in vivo* imaging of CXCR4 to assess the metastatic potential of primaries and metastatic processes.

Ligand development and evaluation
>150 mono- and multimeric pentapeptides were newly synthesized and evaluated in competitive binding assays using [^{125}I]CPCR4 and [^{125}I]SDF-1α as radiolabeled competitors on CXCR4-expressing Jurkat cells and CMS-5 fibrosarcoma cells.

Among others, suitable promising candidates with an affinity in the low nM range were selected for radioiodination, ^{18}F-fluorination and radiometallation (e.g. ^{68}Ga and ^{177}Lu). Biodistribution, quantitative autoradiography and small animal PET imaging was carried out with radioiodinated (*cyclo*(D-Tyr-Arg-Arg-Nal-Gly) CPCR4 and ^{68}Ga-labeled ligands in CMS5-fibrosarcoma or bearing mice (retrovirally transduced cell line for stable CXCR4/GFP expression) and PFP/RAG2 mice with subcutaneously growing NSCLC OH-1 xenografts. Tumors and micrometastases in the lungs were further analyzed by micro-autoradiography and immunohistochemistry.

New Tracers for Imaging CXCR4 Expression
10 peptides showed high affinity to CXCR4 (IC_{50} < 10 nm). Radioiodinated CPCR4 binds with high affinity (K_d: 0.4 ± 0.1 nM) and specificity (>90%) to Jurkat cells and transduced CXCR4/GFP-expressing cells. Radioiodinated CPCR4 showed specific uptake in OH-1 SCLC-tumors. Extremely high focal CXCR4 expression was detected in multiple lung metastases formed in the SCLC tumor model. Approx. 21d after inoculation, metastases were detected ex-vivo with ROI/background ratios of up to 200/1. Although the iodination compound exhibited high hepatobiliary excretion typical for non-optimized peptides, some ^{68}Ga-labeled versions showed excellent *in vivo* properties.

Conclusions
Radiolabeled CXCR4-binding peptides are extremely interesting and promising new tracers for studying metastatic processes in vivo. Further mono- and multimeric constructs of CPCR4 peptides conjugated with chelators and fluorescent agents are currently under investigation.

Research Support
Federal Ministry of Education and Research.

TRITIUM LABELLING OF A NEW TUBERCULOSIS DRUG, AN UNDESIRED ISOTOPE EFFECT AND AN ALTERNATIVE SOLUTION VIA ICP-MS

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Tuberculosis (TB), which kills two million people annually, is surpassed only by AIDS as the most lethal infectious disease. It is tied inextricably to the AIDS epidemic, disrupting in immune-compromised AIDS patients and often killing them before the AIDS virus does. The last TB-specific drug was discovered in 1968 but newer and better drugs are urgently needed to shorten the duration of TB treatment and to reduce the emergence of drug resistance. In 2005 Johnson and Johnson published results of a very promising drug (R207910 or TMC207) to treat TB based on a novel mechanism of action.[1]

Although pharmacokinetic studies in mice are very promising, profound studies of the compound's properties are required before it can enter into clinical development. To support these studies a tritium labelled compound was synthesized, but an undesired isotope effect was observed. Due to this, the data generated by using this radiotracer were not reliable and an alternative approach was needed. A new technique was explored using bromo isotope enriched compound and inductively coupled plasma mass spectrometry (ICP-MS), which showed to be a very powerful alternative for radiotracer technology.[2]

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THE APPLICATION OF ISOTOPE LABELLING WITHIN QUOTIENT BIOSCIENCE

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The Quotient Bioscience Group is organised into three principal businesses; Quotient Bioresearch, HFL Sports Science and Alba Bioscience and is focused on the provision of high value-added analytical and safety evaluation services and products for bioscience and sport.

The core of HFL Sports Science drug testing expertise stems from its long association with equine sport, particularly thoroughbred horseracing. Since the 1960's HFL has continually been involved in pioneering research and development work, contributing to many internationally agreed regulations that underpin the Rules of Racing. This means testing services are always evolving to meet new threats to the integrity of equine sport, to support the welfare of competing horses and to underpin confidence in the betting industry.

An overview will be presented of the analytical techniques used to screen urine and blood samples for the major groups of prohibited substances with particular reference to the use of isotope labelling.

The analytical challenges faced within drug surveillance will also be discussed, including the emergence of biopharmaceuticals.

Other novel applications of isotope labelling within Quotient Bioresearch's Drug Development Services including Bioanalysis, Biomarkers, Metabolism and its own synthetic chemistry group will be highlighted.

TOTAL SYNTHESIS OF ^{14}C-LABELLED PROCYANIDIN B2

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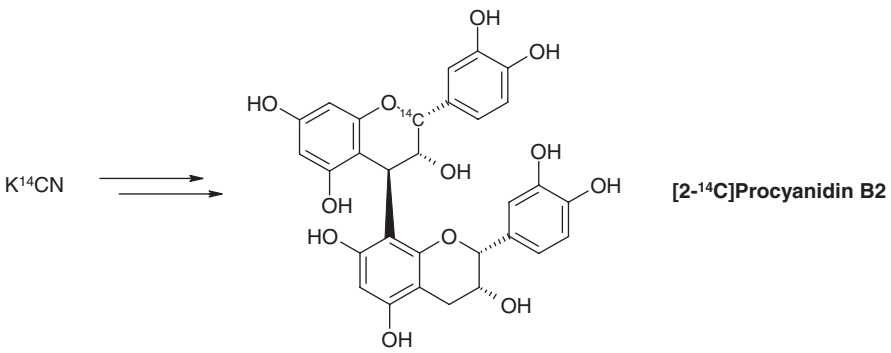
The appealing idea that foods commonly consumed for pure pleasure (such as dark chocolate) could also bring tangible benefits for health is now generally recognised and supported by solid scientific evidence. In this context, polyphenol-rich foods have attracted a wide interest due to their health benefits (e.g. antioxidative activity). Flavan-3-ols and their oligomeric procyanidin forms represent one of the major dietary families of polyphenols; fresh fruits, tea, cocoa and dark chocolate are particularly rich in procyanidins.[1] During the last few decades, many *in vitro* and *in vivo* studies have shown the beneficial effects of procyanidins on health.[2] However, their absorption and metabolism is still not fully understood and some aspects are still controversial.[3] Therefore, to contribute to the study of polyphenol metabolism, we decided to undertake the preparation of ^{14}C-radiolabeled procyanidin B2, one of the major procyanidins present in cocoa and chocolate.



The enantioselective synthesis of [2-^{14}C]procyanidin B2 has been achieved in 17 steps, involving as key steps; the Sharpless dihydroxylation of an elaborated alkene, a stereoselective intramolecular cyclisation to benzylated (+)-[2-^{14}C]catechin, and the condensation of an activated benzylated (−)-[2-^{14}C]epicatechin with a non-labelled benzylated (−)-[2-^{14}C]epicatechin unit to afford procyanidin B2 in protected form. 11 mCi of benzylated procyanidin B2 were thus obtained from 524 mCi of potassium [^{14}C]cyanide in 14 "hot" steps, this material was then kept in the protected form for batch to batch deprotection prior to use in biological assays.

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STRATEGIES FOR ^{3}H-LABELLING OF DECAPEPTIDE HOE 140

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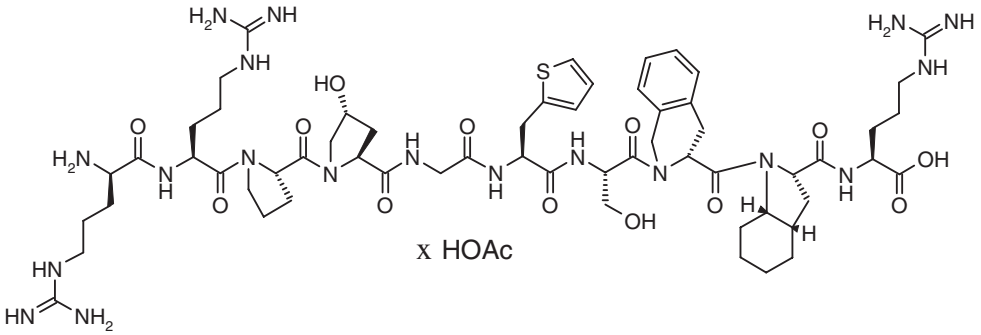
Different strategies for ^{3}H-labeling of decapeptide HOE 140 will be presented. We have evaluated the approach to achieve a maximum specific activity with minimum hot steps in the lab. Neither attempts to introduce the tritium label into the full-length peptide nor the approach to label a single amino acid and to introduce it into the peptide chain were successful. The best way to make the desired compound was to label a large subunit and to build up the complete peptide chain with only a few hot synthetic steps.



HOE 140

METALLATION OF HETEROARYLS AND ITS APPLICATION TO ISOTOPIC LABELLING

PAUL ALLEN,[a] VINCENT COISSARD,[b] DAVE J. WILKINSON,[a] MIKE HICKEY,[a] LEE KINGSTON,[a] and MOYA CAFFREY[a]

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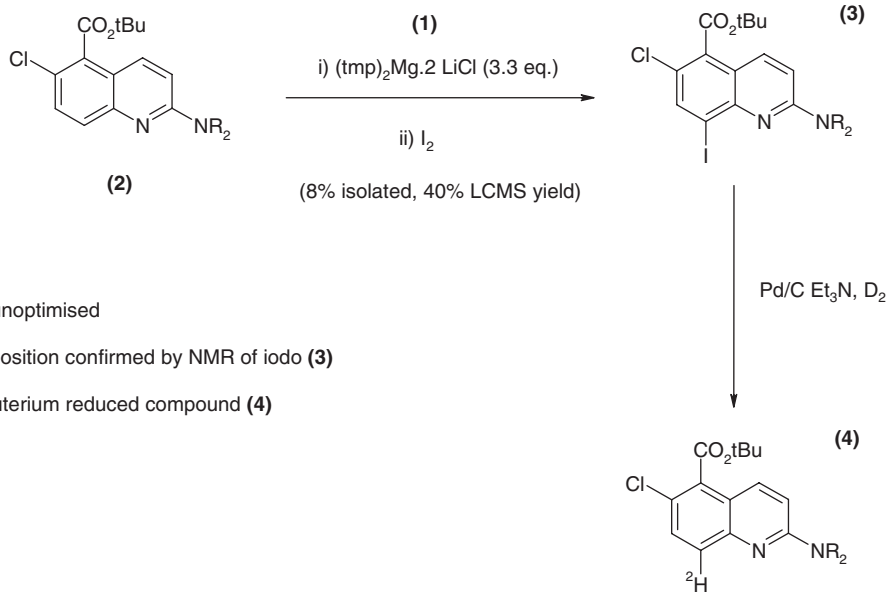
Ready access to isotopically labelled molecules is an important aspect of drug discovery and development. Tritium labelled compounds can be synthesised using either exchange procedures employing a suitable catalyst or via a reductive procedure of a suitable halogenated derivative.

Catalysts such as Crabtree's ([Ir.(cod).(PCy_3).(py)]PF_6) are often employed in exchange procedures as they can be both quick and efficient in the incorporation of isotope into a molecule. However, they do also have drawbacks and can often fail with many complex molecules due to unproductive binding and the need to carry out the exchange reactions in dichloromethane. Of increasing utility is the two-step iodination - reductive dehalogenation procedure which works with a wide variety of activated and deactivated aromatic systems. One potential disadvantage of this approach is the use of strongly acidic conditions e.g. NIS/TFA or triflic acid to introduce iodine into the molecule. However, once the iodinated derivative has been prepared, it can usually be reduced using either deuterium or tritium and the isotope incorporated under very mild palladium-catalysed conditions.

The availability of different chemistries to introduce iodine into both aryl and heteroaryl compounds would provide a very important extension to the above approach. One such method, recently published by Paul Knochel[1], involves the metallation of heteroaryls with magnesium bases such as **1**. The resulting magnesiated species are then reacted with iodine to form a suitable iodo derivative. Compound **1** has been prepared in our laboratory and used to metallate a range of heteroaryls to demonstrate the utility of this approach. This is exemplified by its reaction with the functionalised quinoline **2** and the resultant iodoquinoline **3** thus formed, has been reductively dehalogenated using deuterium to give 8-deutero-quinoline **4**.

Journal of Labelled Compounds and Radiopharmaceuticals



Reference

[1] P. Knochel, G. C. Clososki, C. J. Rohbogner, *Angew Chem Int Ed*, **2007**, *46*, 7681–7684.

THE SYNTHESIS OF SINGLY LABELLED [^{14}C]AROMATIC RINGS

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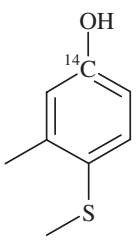
GE Healthcare UK Limited, Amersham Place, Little Chalfont, Buckinghamshire, HP7 9NA, UK

The synthesis of singly labelled [^{14}C]aromatic rings and their use in the study of metabolites by mass spectroscopy will be discussed. Various strategies for the synthesis of singly labelled [^{14}C]aromatic rings will be presented:

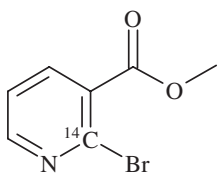
The synthesis of a singly labelled substituted [^{14}C]benzene
The synthesis of 3-methyl-4-thiomethyl[1-^{14}C]phenol from ethyl [3-^{14}C]acetoacetate and 3-buten-2-one, followed by aromatisation and subsequent introduction of the thio-moiety, will be outlined.[1,2]

The synthesis of a singly labelled [^{14}C]aromatic heterocycle
The synthesis of methyl 2-bromo[2-^{14}C]nicotinate using potassium [^{14}C]cyanide as starting material will be described.

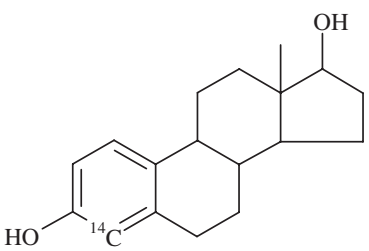
The synthesis of a steroid containing a singly labelled [^{14}C]aromatic ring
Two different approaches to the synthesis of [4-^{14}C]estradiol and their relative merits will be discussed.[3,4]



3-methyl-4-thiomethyl
[1-^{14}C]phenol



methyl 2-bromo
[2-^{14}C]nicotinate



[4-^{14}C]estradiol

References

[1] T. Hirao, M. Mori, Y. Ohshiro, *J Org Chem*, **1990**, *55*, 358.
[2] F. D. Toste, F. LaRonde, I. W. J. Still, *Tetrahedron Lett*, **1995**, *36*, 2949.
[3] J. A. Hartman, A. J. Tomasewski, A. S. Dreiding, *J Am Chem Soc*, **1956**, *78*, 5662.
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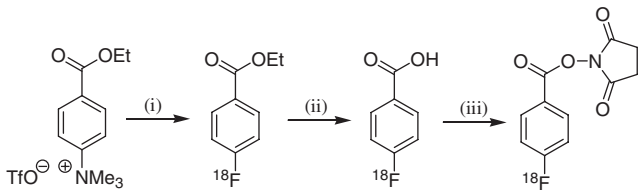
POSTER PRESENTATION ABSTRACTS

THE FIRST SINGLE-STEP-SINGLE-POST SYNTHESIS OF 4-[^{18}F]SFB

RAN YAN,[a] LAURENT BRICHARD,[b] DMITRY SOLOVIEV,[b] FRANKLIN I. AIGBIRHIO,[b] and MICHAEL A. CARROLL[a]*

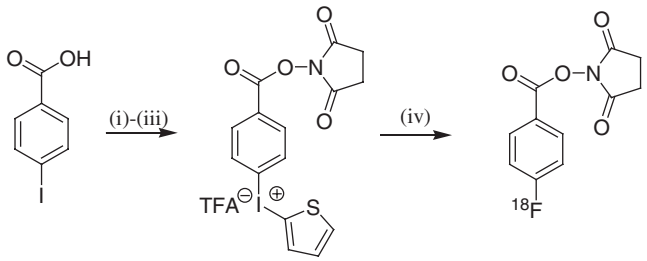
[a]School of Chemistry, Newcastle University
[b]Wolfson Brain Imaging Centre, University of Cambridge

The application of the acylation approach with *N*-succinimidyl 4-[^{18}F]fluorobenzoate ([^{18}F]SFB) is the most versatile method for the incorporation of ^{18}F into peptides, proteins or antibodies. However the radiosynthesis of [^{18}F]SFB requires a laborious three-step procedure, which limits its utilisation.[1] Therefore there is major need for an improved radiosynthetic method.



Scheme 1. (i) $K^{18}F/K_{2.2.2}$; (ii) $NaOH/H_2O$; (iii) coupling reagents (DCC, DSC or TSTU).

Diaryliodonium salts have been shown to be suitable precursors for single-step nucleophilic [^{18}F]fluorination of arenes without the need of further activating groups. It was then of interest to use this approach for the radiosynthesis of [^{18}F]SFB. In this case particular salts containing the 2-thienyl group enable highly regioselective ^{18}F-fluorination. The required precursor, (4-((2,5-dioxopyrrolidin-1-yloxy)carbonyl)phenyl)(thiophen-2-yl)iodonium trifluoroacetate, was synthesised in three steps with an un-optimised yield of 26%.[2,3] The precursor was then subjected to ^{18}F-fluorination. Radio-HPLC analysis indicated that [^{18}F]SFB was formed in radiochemical yields of 13–23% ($n = 4$).



Scheme 2. (i) TSTU, TEA, DMF, 2 h, 82%; (ii) $(Bu_3Sn)_2$, $Pd(PPh_3)_4$, PhMe/DMF, Δ, 24 h, 48%[3] (iii) diacetoxyiodo-2-thiophene, TFA, CH_2Cl_2, −30°C to R.T., 24 h, 26%; (iv) $K^{18}F/K_{2.2.2}$, TEMPO, DMF, 5 min.

For the first time, a simple single-step method for the radiosynthesis of the prosthetic radiolabelling reagent [^{18}F]SFB has been developed. Optimisation of the radiochemical yield is on-going.

References

[1] S. M. Okarvi, *Eur J Nucl Med*, **2001**, *28*, 929.
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[3] J. L. Sessler, B. Wang, A. Harriman, *J Am Chem Soc*, **1995**, *117*, 704.

Journal of Labelled Compounds and Radiopharmaceuticals

THE FIRST SYNTHESIS OF ETHYL 3-[^{18}F]FLUOROBENZOATE USING [^{18}F]FLUORIDE

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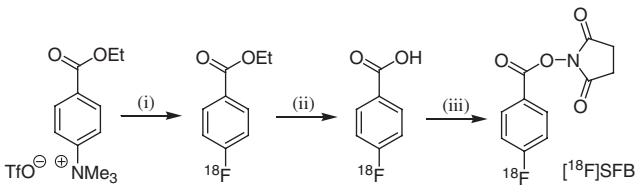
[b]Wolfson Brain Imaging Centre, University of Cambridge

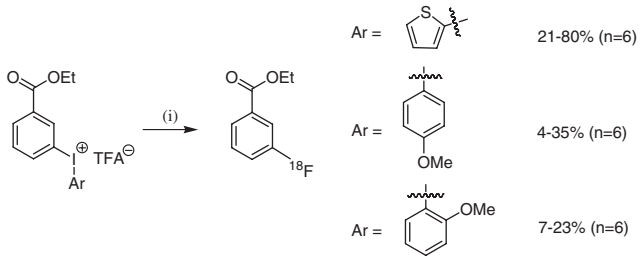
Ethyl 4-[^{18}F]fluorobenzoate is a key precursor to *N*-succinimidyl 4-[^{18}F]fluorobenzoate ([^{18}F]SFB), the most versatile method for the incorporation of ^{18}F into peptides, proteins or antibodies.[1] Currently the [^{18}F]fluorine is restricted to the 4-position, as it is introduced by a S_NAr process (Scheme 1) from which the more stable 3-regioisomer is not available. Therefore there is a need for access to this material to enable SAR studies to contribute to the optimisation of a radiopharmaceutical labelled in this way.

Diaryliodonium salts have been shown to be suitable precursors for single-step nucleophilic [^{18}F]fluorination of arenes without the need of further activating groups and with little or no restriction on the nature of the functionality present.[2,3] It was then of interest to use this approach for the radiosynthesis of the ethyl 3-[^{18}F]fluorobenzoate. The appropriate 3-iodonium salts were prepared from ethyl tributylstannylbenzoates and a range of aryliodobis(acetates) and then subjected to ^{18}F-fluorination. Radio-HPLC analysis indicated that the 2-thienyl iodonium salt is the best precursor under our routine screen conditions for the radiosynthesis of ethyl 3-[^{18}F]fluorobenzoate with a yield range of 21–80% ($n = 6$).

For the first time, a simple single-step method for the radiosynthesis of ethyl 3–[^{18}F]fluorobenzoate has been developed. Optimisation of the radiochemical yield for all isomers is on-going.



Scheme 1. (i) $K^{18}F/K_{2.2.2}$; (ii) $NaOH/H_2O$; (iii) coupling reagents (DCC, DSC or TSTU).



Scheme 2. (i) $K^{18}F/K_{2.2.2}$, TEMPO, DMF, 5 min.

References

[1] S. M. Okarvi, *Eur J Nucl Med*, **2001**, *28*, 929.
[2] M. A. Carroll, J. Nairne, G. Smith, D. A. Widdowson, *J Fluorine Chem*, **2007**, *128*, 127.
[3] M. A. Carroll, R. Yan, F. I. Aigbirhio, L. Brichard, D. Soloviev, *J Nucl Med*, **2008**, *49S*, 303P.

ENHANCED ON-LINE DETECTION FOR RADIOCHEMICAL MEASUREMENT

KEITH A HALL, and HUW LOARING

LabLogic Systems Limited, Paradigm House, 3 Melbourne Avenue, Broomhill, Sheffield S10 2QJ, UK

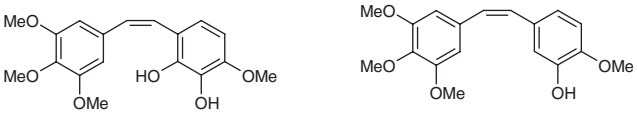
Recent moves towards the use of increasingly lower levels of radioactivity in samples for metabolite profiling whilst still favouring the speed and convenience of on-line detection have led to the development of SoFie. On-line radio detection of compounds separated by both HPLC and the newer fast LC/Rapid resolution techniques remains an important tool for researchers. The challenge is to detect ever decreasing levels of activity whilst remaining in the highly controlled and regulated environment of the trusted software systems. Here we show that the new SoFie system, controlled by the Laura radio chromatography system offers up to 8 times the level of sensitivity of standard on-line detection. This eliminates the need for fraction collecting which is always time consuming and potentially destructive to the delicate sample as further processing is required for counting on plate readers. The SoFie system also offers enhanced resolution as well as improved limits of detection.

SYNTHESIS OF ^{14}C-LABELED COMBRETASTATIN A-1 DIPHOSPHATE ([METHYL-^{14}C]COMBRETASTATIN A-1 DIPHOSPHATE)

RODNEY T. BROWN,[a] VICTOR L. MURRELL,[a] KEVIN G. PINNEY,[b] MADHAVI SRIRAM,[b] DAVID J. CHAPLIN,[c] and SUMAN SHARMA[c]

[a]Almac Sciences, 20 Seagoe Industrial Estate, Craigavon, BT63 5QD, N. Ireland, UK
[b]Department of Chemistry and Biochemistry, Baylor University, One Bear Place #97348, Waco, TX 76798–7348, USA
[c]OXiGENE Inc., 230 Third Avenue, Waltham, MA 02451, USA

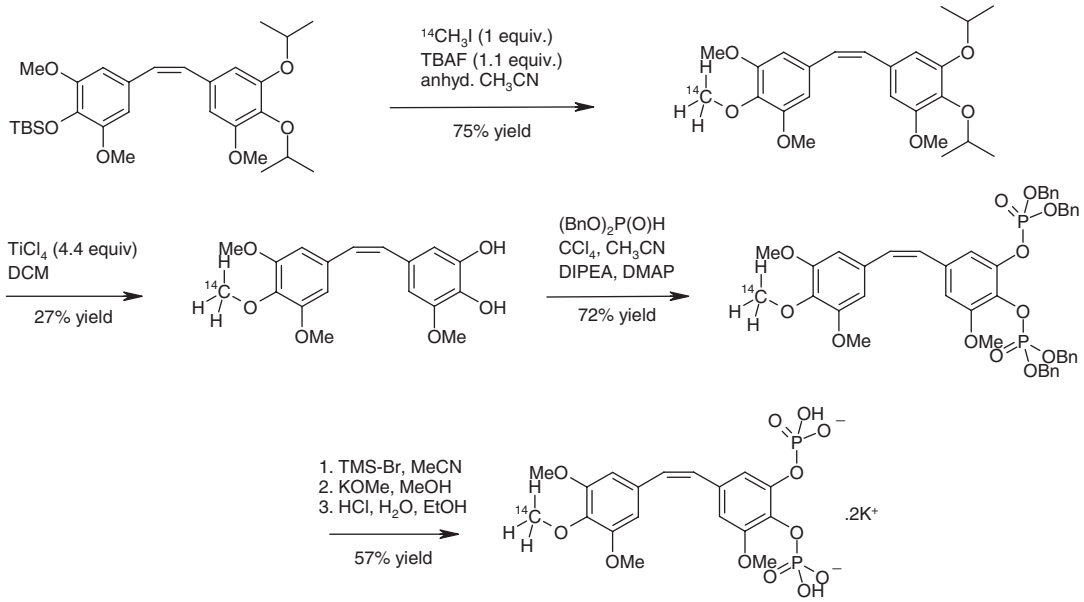
Combretastatin A-1 and Combretastatin A-4 are two microtubule depolymerising agents, first isolated from the African bush willow tree by Pettit and coworkers in the early 1980's.



Combretastatin A-1 **Combretastatin A-4**

OXiGENE Inc. (Waltham MA) is currently developing phosphate prodrugs of these compounds as vascular disrupting agents for the treatment of cancers, particularly solid tumours.

This poster reports the synthesis of [methyl-^{14}C]Combretastatin A-1 diphosphate using the route shown below.



[methyl-^{14}C]-Combretastatin A1 diphosphate

Using this route 20 mCi of the desired target were prepared in excellent chemical and radiochemical purity with an overall radiochemical yield of 8.4%.

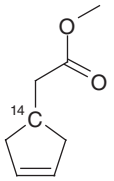
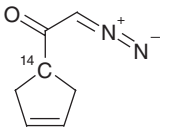
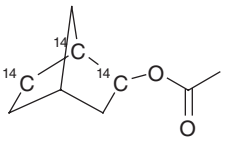
THE COLOGICA LABELLED COMPOUNDS DATABASE©

WILLIAM J. S. LOCKLEY

CoLogica Scientific, 92, Loughborough Rd, West Bridgford, Nottingham, NG2 7JH, UK

The labelled compound database described in the poster covers compounds labelled with isotopes of carbon and hydrogen, ^{2}H,^{3}H,^{11}C,^{13}C & ^{14}C. It contains the main fields of interest to chemists involved in isotopic synthesis.

The database is extensive, containing tens of thousands of records, but is not comprehensive. It comprises of abstract records from both the early and the recent isotopic synthesis literature. It particularly concentrates on literature which is not easily retrieved by search engines and hence includes many records from sources such as local and international IIS symposium proceedings and from the classic text books on isotopic synthesis, many of which are now out of print. As such, the database is a rapid and useful adjunct to searching via the major search engines. The accent is on molecules likely to be of use as intermediates. A typical abstract record is shown below.

Labelled compound	Precursor(s)	Target	Other Reagent(s)
			Ag_2O MeOH

Name	Abundance	Yield
Methyl 2-([4-14C]Cyclopenten-4-yl)-acetate, methyl ([1-14C]cyclopent-3-en-1-yl)acetate.		Used directly

Reaction Conditions	Other Data	ID
The rearrangement is typically carried out on the diazoketone (often from the acid chloride via CH2N2) with freshly prepared Ag2O. For related chemistry see K Murdock, B Angier, J Org Chem, 27, 2935 (1962).	Wolff variant of the Arndt-Eistert rearrangement. The intermediate is probably the ketene.	13278
		Donor 14CCH(CO2R)2

Reference	Code
C J Collins, C E Harding, Ann Chem, 745, 124 (1971). Also reported in "Organic Synthesis with Carbon-14", R R Muccino, Wiley Interscience, John Wiley and Sons, New York, p461, 1983. [ISBN 0-471-05165-9]	14CRM

The top four structure fields are searchable by structure and sub-structure (including via isotope and isotope position). Moreover, all the other nine text fields are string searchable.

The database is constructed around the Symyx MDL IsisBase® platform, and has a simple flat architecture, well suited to integration with other structure-based databases or with the in-house record systems of isotopic synthesis groups.

Two typical uses of the database are exemplified in the poster. These show typical hits returned by (a) a search for approaches to ^{14}C-labelling via nucleophilic displacement of halides by $^{14}CN^-$ and (b) a search for methods to achieve *ortho*-labelling of nitroaromatics with ^{3}H.

NOVEL PROTOCOL FOR SOLID PHASE SYNTHESIS OF RADIO-IODINATED LIGANDS FOR IMAGING OF CANNABINOID RECEPTORS IN THE BRAIN

CHIH-CHUNG TSENG, BINGLI MO, and ALAN C. SPIVEY*

Department of Chemistry, Imperial College, London, SW7 2AZ, UK

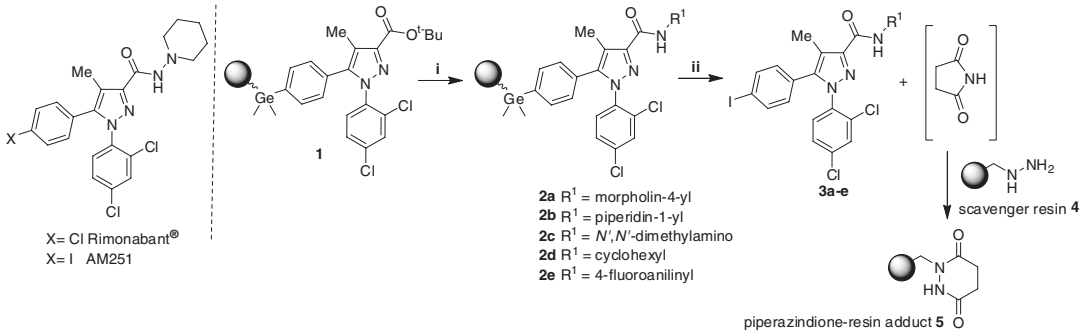
Sanofi-Aventis' rimonabant® is a CB1 (cannabinoid) receptor antagonist indicated for the treatment of obesity, metabolic syndrome, addiction and smoking cessation.[1] Radiolabelled analogues are potential Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT) imaging agents for visualising the distribution of cannabinoid receptors in the brain for medical research. Conventional methods for the preparation of radio-iodinated cannabinoid receptor ligands employ organostannane precursors which undergo electrophilic *ipso*-iododestannylation with concomitant formation of toxic organostannane by-products. Rigorous removal of organostannane residues and other organic by-products (*e.g.* *p*-toluenesulfonamide from dichloroamine-T) are necessary prior to injection of the ligand for *in vivo* experiments.[2]

This poster will outline a novel, non-toxic and straightforward approach for the parallel solid-phase synthesis of iodinated cannabinoid receptor ligands **3a**-**e** based on the diarylpyrazole skeleton of rimonabant (Scheme 1).[3]

Upon subjection of the functionalised resins **2a-e** under iodination conditions, iodinated analogues **3a**-**e** were obtained in good yields (42–63%) and the concomitantly released succinimide was removed *in situ* by treating the crude product mixture with hydrazine-functionalised scavenger resin **4** to give piperazindione-resin adduct **5** leaving just the desired ligands in solution. The purity of these iodinated ligands was quantified in the case of compound **3b** (AM251) by HPLC (UV detection at 250 nm). The chromatogram revealed the presence of just the clean iodinated product as expected.

Moreover, when resin **2b** was subjected to the *ipso*-iododegermylation conditions for just 5 min, iodinated analogue **3b** was obtained in 8% yield which augurs well for the use of this technique for the preparation of the radiolabelled rimonabant analogues within a short reaction period to avoid attenuation of radio-activity [$t_{1/2}$ (^{123}I) 13.2 h, $t_{1/2}$ (^{124}I) 4.2 d].

In conclusion, a novel protocol for rapid and parallel preparation of cannabinoid receptor antagonists has been developed without hazardous metal waste involved. Upon transamidation of resin **1** with a diverse set of amines or hydrazines under basic conditions, iodinated rimonabant analogues were afforded in good yields and purity. This protocol should prove suitable for the rapid preparation of libraries of radiolabelled cannabinoid receptor antagonists for *in vivo* studies.



Scheme 1. Parallel synthesis of cannabinoid receptor ligands **3a-e** through *ipso*-iododegermylation. *Conditions:* **i**) R^1NH_2, LHMDS, 16 h; **ii**) NaI, NCS, TFA-HOAc (1:3 *v/v*), 1 h.

References

[1] M. Rinaldi-Carmona, F. Barth, M. Hkaulme, D. Shireb, B. Calandrab, C. Congy, S. Martinez, J. Maruani, G. Neliat, D. Caputb, P. Ferrarab, P. Soubrie, J. C. Brelike, G. L. Fura, *FEBS Lett*, **1994**, *350*, 240–244.
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[3] A. C. Spivey, C.-C. Tseng, T. Jones, A. Kholer, G. Ellames, Manuscript in preparation.

A GENERAL METHODOLOGY FOR THE SYNTHESIS OF SUBSTITUTED PHENOLS FROM PYRANONE PRECURSORS

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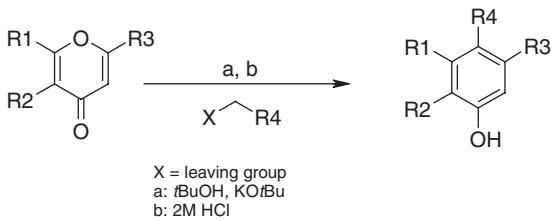
[b]GSK Medicines Research Centre, Gunnels Wood Road, Stevenage, SG1 2NY, UK

Phenols are an important group of aromatic compounds in natural product chemistry. Traditionally, substituted benzenes were obtained by the functionalisation of aromatic rings by reactions such as nitration, sulfonation, reduction and oxidation, often leading to ''*ortho-meta-para*'' mixtures. Synthetic methods for the introduction of the hydroxyl group to aromatic rings are limited, as direct introduction by electrophilic substitution is difficult. Some synthetic routes to phenols include diazotisation, hydroboration, nucleophilic aromatic substitution, Bayer-Villiger reactions and modern catalysis-based methods such as C-H activation.[1,2] However, there is still a need for new synthetic routes to phenols, particularly from acyclic precursors, that would be useful for isotopic labelling.

Construction of the aromatic ring from acyclic precursors can be carried out with the substituents already in place. This method avoids the problems of directing effects that can hamper traditional electrophilic substitution strategies. It also offers potential routes to natural products which contain the susbstituted phenol moiety, as the ring-synthesis method can be used to build up the ring from non-aromatic substrates. This gives the potential to synthesise isotopically labelled natural products from labelled small molecules which are more widely available than uniformly-labelled aromatic rings.

Heterocyclic systems such as pyranones are an excellent source of phenols, as they are susceptible to nucleophilic attack followed by hydrolysis to yield aromatic compounds. The syntheses of various substituted phenols from pyranone precursors, namely 4*H*-pyran-4-one, 3-(benzyloxy)-2-methyl-4*H*-pyran-4-one (*O*-benzyl maltol), 2,6-dimethyl-4*H*-pyran-4-one and diethyl 4-oxo-4*H*-pyran-2,6-dicarboxylate (diethyl chelidonate) are presented. These syntheses employ the use of our developed methodology, reacting the pyranone with a variety of pronucleophiles in the presence of potassium *tert*-butoxide as base and *tert*-butanol as solvent, using conventional heating methods.[3,4] The use of microwave irradiation was found to be beneficial to many of these reactions, with higher yields being observed in the majority of cases–most importantly in those reactions which proved to be the most problematic under conventional heating. Microwave-assisted reactions also showed a significant reduction in reaction times.



References

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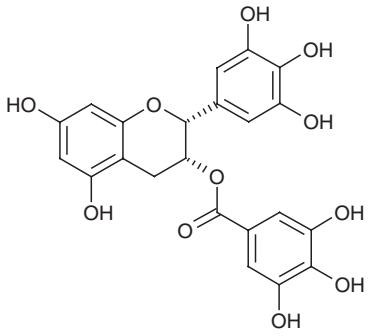
Journal of Labelled Compounds and Radiopharmaceuticals

FIRST SYNTHESIS OF [1,3,5-$^{13}C_3$]GALLIC ACID

LAURA J. MARSHALL,[a] KARL M. CABLE,[b] and NIGEL P BOTTING[a]

[a]School of Chemistry, University of St Andrews, North Haugh, St Andrews, Fife, KY16 9ST, UK
[b]GSK Medicines Research Centre, Gunnels Wood Road, Stevenage, SG1 2NY, UK

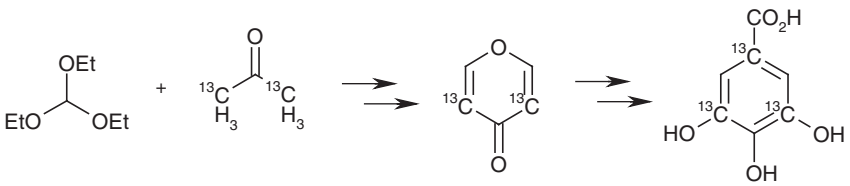
Gallic acid is a phenolic plant metabolite which is normally encountered in plant tissues in ester form. These esters include a group of catechins with antioxidant properties which are found in green tea. Epigallocatechin-3-gallate is the most abundant catechin in green tea and has been shown to inhibit carcinogenesis.[1,2]



(-)-epigallocatechin-3-gallate

Ongoing biological studies into the absorption, metabolism and bioavailability of tea catechins require accurate quantification of the compounds in plasma samples. LC-MS and GC-MS are common techniques used for analysis due to their ability to separate and quantify subnanomolar quantities of an analyte in complex matrices. However, the sensitivity of the mass spectrometer is not constant and therefore calibration is required using an internal standard. The ideal internal standard would be a stable isotope labelled analogue of the analyte as it will have similar chemical and physical properties as the analyte. New synthetic routes to isotopically labelled catechins are therefore required.

An efficient and high-yielding synthesis for [1,3,5-$^{13}C_3$]gallic acid from non-aromatic precursors is presented. [3,5-$^{13}C_2$]4*H*-Pyran-4-one was first prepared from the reaction between triethyl orthoformate and [1,3-$^{13}C_2$]acetone.[3] The third ^{13}C-atom was introduced into the ring by reaction of the pyranone with diethyl [2-^{13}C]malonate.[4,5] The resulting ethyl 4-hydroxy-[1,3,5-$^{13}C_3$]benzoate was brominated in the 3- and 5-positions to give ethyl 3,5-dibromo-4-hydroxy-[1,3,5-$^{13}C_3$]benzoate. Subsequent hydrolysis of the ester and substitution of the bromine atoms with hydroxyl groups was achieved under basic conditions in a single step to yield the desired [1,3,5-$^{13}C_3$]gallic acid. The synthesis of [2,6,-$^{13}C_2$]4*H*-pyran-4-one is also presented to demonstrate the potential of the methodology for the regioselective placement of ^{13}C-atoms into the ring.



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AUTOMATED [^{11}C]ACETATE SYNTHESIZER–SIMPLE WAY TO RELIABLE GMP COMPLIANT MANUFACTURE OF PROSTATE CANCER PET IMAGING RADIOTRACER

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Imaging of prostate cancer by Positron Emission Tomography is a challenging task due to proximity of prostate to the urinary bladder, which is the major route of elimination from a human body for most of the widely used PET imaging radiotracers. Acetate

labelled with carbon-11 has recently been shown to have a potential in imaging different malignancies, with special emphasis on prostate cancer imaging. Newly emerging data on acetate being a substrate for Fatty Acid Synthase underpin usefulness of [^{11}C]acetate in targeting the *de novo* lipogenesis, which is up-regulated in many types of neoplasms.[1] Reliable supply of radiolabelled acetate is an essential component of success in the use of PET in clinical research and clinical diagnostics, being not restricted to prostate cancer.

We set to develop a simple automated device for efficient radiosynthesis of [^{11}C]acetate following the Good Manufacturing Practices guidelines, which would provide the reliable production of the tracer with a possibility to make back-to-back productions with minimal staff exposure. The process was based on a previously published "captive solvent" procedure.[2] One of the aims was to make the synthesizer independent on the type of the cyclotron used for isotope production.

[^{11}C]Carbon dioxide produced by a cyclotron was trapped at room temperature on a molecular sieve trap inside the synthesizer. After the radioactivity from the cyclotron was transferred, the synthesizer released [^{11}C]CO_2 into the reaction loop pre-conditioned with the thin layer of methylmagnesium chloride. Radiolabelling reaction was instant in these conditions and immediately after the end of [^{11}C]CO_2 release the intermediate crude radiolabelling mixture was hydrolysed by an excessive amount of water for injections and purified by means of the solid-phase extraction cartridges. The chemically (and radiochemically) pure [^{11}C]acetate was retained by an anion exchange cartridge. The final formulation of radiotracer was performed directly into the injection vial by detaching [^{11}C]acetate by the sterile physiologic saline solution and passing it through the 0.22 μm sterilising filter. All the components of the synthesizer which were in contact with the final product were made of single use sterile materials.

A sterile injectable solution of [^{11}C]acetate was obtained in less than 10 min after the End of Bombardment with a mean 99% radiochemical purity and better than 95% reliability. The automated synthesizer allows safe back-to-back manufacture of Ph.Eur. grade [^{11}C]acetate in GMP conditions with high reliability.

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