Issue 7 | July 2014

Key Organics Newsletter

Chemistry | Innovation | Quality

On 27th May we announced our new exclusive and global co-marketing agreement with Cambridge Research Biochemicals ("CRB") that further extends our BIONET peptide collection to now include a range of novel microbial peptides. With next day delivery and assured quality, our new peptide portfolio is now available for same day dispatch.

Within our technology section, we profile two areas within our BIONET R&D Department and Services Team; (i) within our BIONET product group we now offer a range of the Soloshonok Ligands from which the derived Nickel complexes allow the synthesis of both known and novel α-amino acids, and (ii) we profile our expanding capabilities in radiochemistry within a case study involving the synthesis of [$^{2}H_{4}$]-Linagliptin, the labelled form of the DPP-4 inhibitor. We also interview Dr. Kerri Stenning who works within our Chemistry Services team and profile our Q3 event attendance; we hope to meet you at one soon!

Key Finder™ New Kinase Library

Our collaboration with Prosarix continues to expand and we have now applied our Key Finder™ platform to kinase inhibitor discovery. It combines:

- A novel function (Kscore) for scoring hinge binding moieties based on Extended Huckel Theory;
- Generation of a synthetically tractable large virtual library using available in-house reagents (>14 million compounds) that include both known and novel cores; and
- Structure based virtual screening protocols to select compounds with desired selectivity and potential for optimisation.

Following selection, compounds can be rapidly synthesised for assay. The library has been validated *in silico* against observed Kinase structural variation (e.g. DFG-in, DFG-out states and selectivity pockets). Please contact us for our new information sheet or visit our website.

New Peptide Alliance with CRB

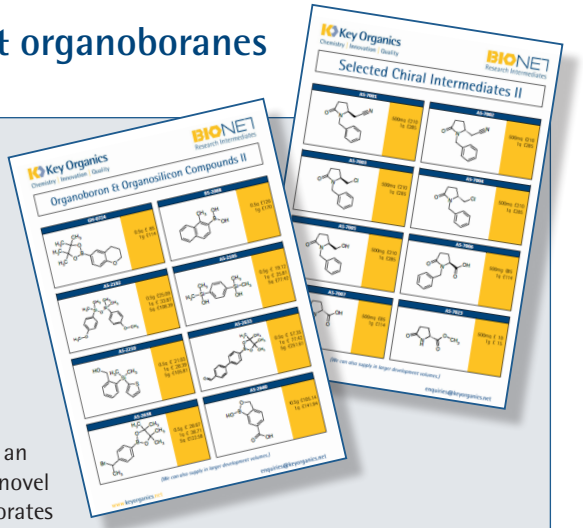
Our new alliance with CRB provides an example of our successful co-marketing partnership model which complements other deals that we have established with with Pareon Chemicals Ltd, Advanced Molecular Technologies Pty Ltd. and Almac Ltd. Key Organics will stock and market the entire range of CRB new antimicrobial peptides within our BIONET product group for worldwide distribution together with the provision of customer and technical services for scale-up and longer-term supply. **For more information, please visit our website at www.keyorganics.net**

BIONET New chiral intermediates & organoboranes available from BIONET

Our new information sheet and web updates profiles our increasing collection of chiral intermediates that are all available for same day dispatch and available in research and development quantities. All products are available with full CoA including 400 MHz nmr and LC-MS data to verify their purity (>97% & >99% e.e.). With access to a broad range of new catalysts and separation technologies, we can now offer a larger number of current and novel chiral molecules at development quantities.

Our co-marketing agreement with AMT continues to generate an increasing number of novel and versatile organoborates for C-C cross coupling.

Our new information sheet is available online at: **www.keyorganics.net**



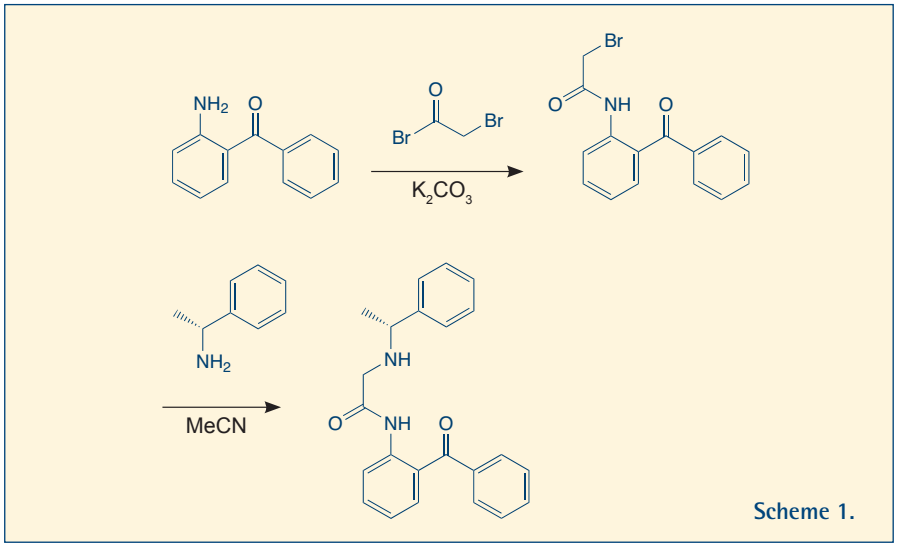
Our premium BIONET product range continues to grow toward our target of 100,000 with the same guarantees that you can rely on.

Advancements in amino acid synthesis: Chiral resolution of amino acids using the 'Soloshonok Ligands'.

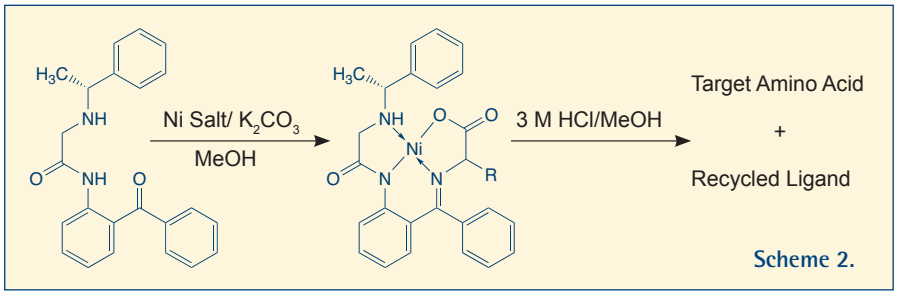
Since the beginning of organic chemistry, α-amino acids have been an attractive target for synthetic chemists. Here we discuss a cost-effective procedure for the chemical synthesis of enantiomerically pure amino acids. Ikerbasque Research Professor Soloshonok and his team at the University of the Basque Country have developed and refined a method of chiral resolution via Nickel (II) Schiff base complexes[1,2,3,4]. The source of chirality comes from an inexpensive chiral auxiliary, 1-(phenyl)ethylamine, incorporated into specially designed ligands (Scheme 1).

The diastereomerically pure Ni(II) complexes, a result of the configurational stability of the stereogenic nitrogen atom (Scheme 2) were disassembled to produce enantiomerically pure target amino acids, along with the recycled chiral ligand.

The synthesis of the ligands involves a set of very simple reactions occurring with high yields. To prepare the Ni(II) complexes; the ligands are heated in MeOH in the presence of the amino acid, a Ni salt and K_2CO_3. The reaction mixtures are then poured into water and the products are simply filtered off, dried and purified by column chromatography. The material obtained is then stirred in 3M HCl in MeOH at 50°C for 4 hours. The mixture is then poured onto water and the ligand is recycled. The desired amino acid can then be isolated via workup on an ion exchange column.



Scheme 1.



Scheme 2.

All reactions are conducted under operationally convenient conditions, featuring high yields and thus underscoring the attractive cost structure of this method. Therefore this must draw comparisons with enzymatic processes for the manufacture of amino acids. Although the presented approach has a key benefit over rival processes, in that the procedure actually requires little technical expertise and is not particularly intricate. The approach can be reliably reproduced and is particularly useful where both enantiomers of a given amino acid are required.

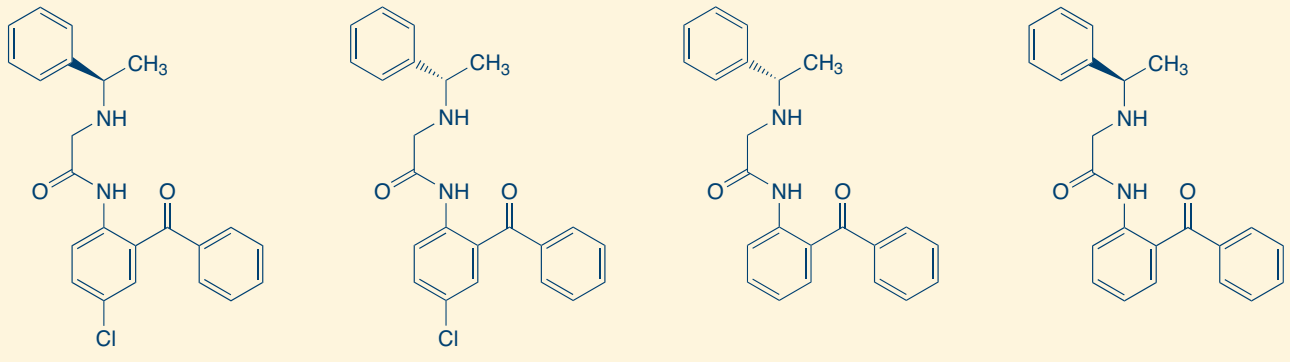
We envisage that at medium scale the route to pharmaceutically important building blocks such as (*S*)-2,6-Dimethyltyrosine could actually be much simpler, faster and cheaper via this method. The current literature method involves making the pro-chiral dehydroaminoacid substrate; (*Z*)-2-acetamido-3-(4-acetoxy-2,6-dimethylphenyl)-prop-2-enoate (4-steps), which is reduced via asymmetric hydrogenation using a Rhodium catalyst, followed by deprotection using HCl.

The Soloshonok Ligands, Key Features:

- Recyclable
- Simple to use
- Cost effective
- Can be performed under operationally convenient conditions
- High yields and enantiomeric excess
- Reproducible

A selection of Soloshonok Ligands are available from Key Organics stock and ready for same day shipping (*Figure 1*).

Figure 1. New Soloshonok Ligands now available from Key Organics



References:

1. A. Sorochinsky, H. Ueki, J. Aceña, T. Ellis, H. Moriwaki, V. Soloshonok, Org. Biomol. Chem, 2013, 11, 4503-4507
2. J. Wang, H. Liu, J. Aceña, D. Houck, R. Takeda, H. Moriwaki and V. Soloshonok, Org. Biomol. Chem, 2013, 11, 4508-4515
3. A. Sorochinsky, J. Aceña, H. Moriwaki, T. Sato, V. Soloshonok, Amino acids, 2013, 45, 5, 1017-33
4. H. Moriwaki, D. Resch, H. Li, I. Ojima, R.Takeda, J. Aceña, V. Soloshonok, Amino Acids. 2014, 46, 945-52

Key Organics
Chemistry Services

Key Organics' Chemistry Services team offers bespoke synthesis solutions on an FTE/Research (fee-for-service) or one-off custom synthesis (fee-for-compound) basis. Offering a customer driven synthetic organic chemistry service on mg-small kg scale, our core competencies cover chemistries as diverse as heterocyclic chemistry, chiral chemistry, high pressure reactions, focused arrays for hit explosion or hit-to-lead optimisation, etc, and we undertake research projects in the areas of medicinal chemistry, agrochemistry, petrochemistry, aromachemicals, etc.

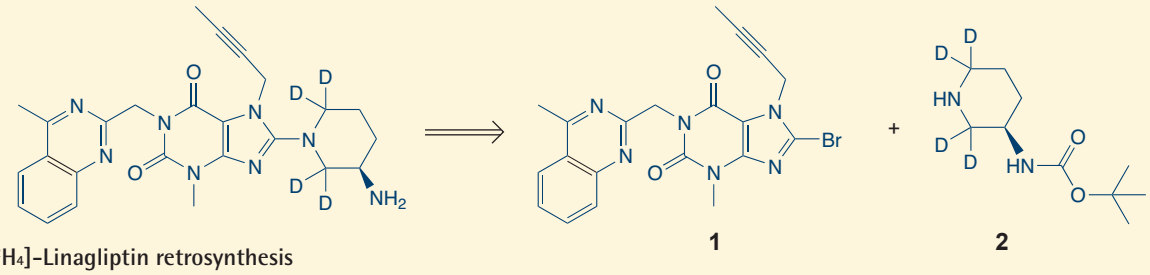
Our growing expertise in Radiolabelled API's and Intermediates

One currently popular area for our clients is the synthesis of cold (non-radioactive) labelled reference standards. These materials are of use as tracers in the modeling of a number of chemical and biochemical systems, for example, in tracking the passage of an isotope, or an atom with a variation, through a reaction, metabolic pathway, or cell. The reactant is 'labeled' by replacing specific atoms by their isotope. The position of the isotopes in the products is measured to determine the sequence the isotopic atom followed in the reaction or the cell's metabolic pathway.

[$^2H_4$]-Linagliptin Case Study

We have developed considerable experience in the synthesis of ^2H- (deuterium) and ^{13}C-labelled materials. Whilst it is often possible to identify a suitably labelled commercially available building block with which to replicate the known non-labelled chemistry, there are instances where we need to devise an alternative synthesis route. Two such examples are to facilitate the late stage incorporation of the label, minimising the quantity – and cost – of material required, or where an appropriate building block is not available from the commercial pool.

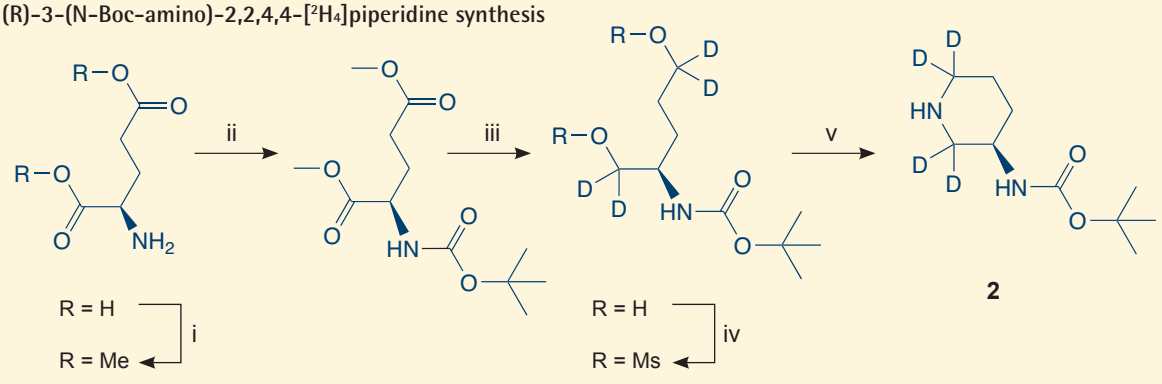
In one particular example, a customer required gram scale quantities of [$^2H_4$]-linagliptin. Linagliptin (CAS 668270-12-0) is a DPP-4 inhibitor developed by Boehringer Ingelheim for treatment of type II diabetes.[1] The availability of the late stage bromoimidazole building block **1** suggested placing the labelled atoms in the aminopiperidine component **2** (Scheme 3).



Scheme 3: [$^2H_4$]-Linagliptin retrosynthesis

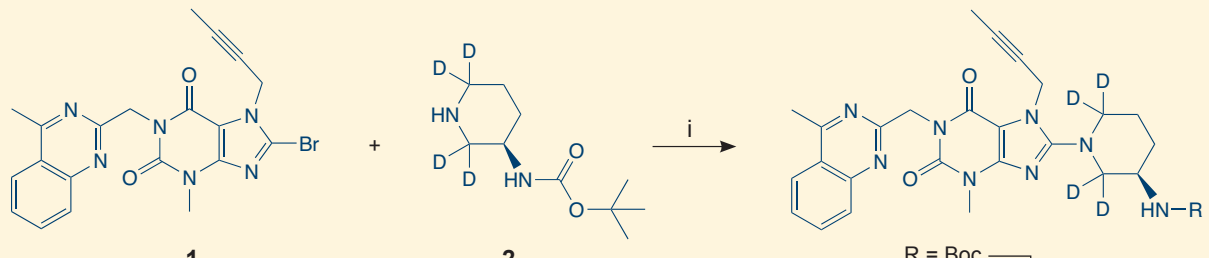
Adaption of a known method for the synthesis of enantiomerically pure 3-amino cyclic amines afforded the required building block (Scheme 4).[2] Commercial D-glutamic acid was esterified and N-Boc protected. Reduction of the two ester functions to the corresponding alcohols proceeded cleanly with sodium borohydride, and no loss of the Boc group was observed. Utilising the corresponding [$^2H_4$]-reductant afforded the chiral [$^2H_4$]-diol, which was converted to the bis-mesylate and cyclised to (R)-3-(N-Boc-amino)-2,2,4,4-[$^2H_4$]piperidine on treatment with ammonia.

Scheme 4: (R)-3-(N-Boc-amino)-2,2,4,4-[$^2H_4$]piperidine synthesis



Reagents: (i) c. H_2SO_4, MeOH; (ii) Boc_2O, Et_3N, Dioxane, H_2O; (iii) $NaBD_4$, $CaCl_2$, EtOH; (iv) MsCl, Et_3N, CH_2Cl_2; (v) NH_4OH, MeCN

With gram quantities of the labelled building block in hand, the synthesis of [$^2H_4$]-linagliptin was completed via reaction of the customer supplied bromoimidazole building block **1** with the aminopiperidine component **2**, followed by Boc-deprotection (Scheme 5).[1]



Scheme 5: [$^2H_4$]-Linagliptin synthesis

Reagents: (i)K_2CO_3, DMF; (ii) TFA, CH_2Cl_2

References:

1. M. Eckhardt, E. Langkopt, M. Mark, M. Tadayyon, L. Thomas, H. Nar, W. Pfrengle, B. Guth, R. Lotz, P. Sieger, H. Fuchs and F. Himmelsbach, *J. Med. Chem.*, 2007, **50**, 6450-6453
2. S.-H. Moon and S. Lee, *Syn. Commun.*, 1998, **28**, 3919-3926

Events that we will attend during Q3 2014

2nd – 4th July
RICT 2014
http://www.ldorganisation.com/v2/page/rict_2014_international_conference_medicinal_chemistry/products.html

3rd September
Peakdale Symposium
http://www.peakdale.co.uk/news-events/peakdale-symposium-2014.html

8th - 9th September
Nordic Life Science Days
http://www.nlsdays.com/

7th – 11th September
XXII International symposium on Medicinal Chemistry
http://www.ldorganisation.com/v2/produits.php?langue=english&tcle_menus=1238915495&tcle_data=1238740790

15th – 18th September
Chemoutsourcing
http://www.chemoutsourcing.com/index.php

21st – 24th September
Fragment-based Lead Discovery Conference 2014, Basel, Switzerland
http://www.ysbl.york.ac.uk/fbld/2014/

22nd -23rd September
SCI: A Celebration of Organic Chemistry
https://www.soci.org/Events/Display-Event.aspx?EventCode=FCHEM143

30th September
SCI: Secrets of Success: CRO Views of Successful Outsourcing
https://www.soci.org/Events/Display-Event.aspx?EventCode=FCHEM430

Staff Interview

Dr. Kerri Stenning

Q: Please tell us a bit about yourself?

A: I grew up in Surrey and completed my undergraduate degree at the University of Reading, obtaining an MChem in Chemistry that included a year industrial placement at GlaxoSmithKline in Stevenage. I then moved to the University of Southampton for my PhD which focussed on radical methodology and its application to natural product synthesis. I have worked at Key Organics since completing my PhD in 2011.

Q: What is your role within Key Organics?

A: I originally joined Key Organics as a chemist in the Biochemicals and Fragment team, synthesising novel compounds in these product ranges. I then moved to the FTE/Custom synthesis team where I design and carry out the synthesis of compounds to a clients specification.

Q: What do you enjoy about working at Key Organics?

A: The variety in the work. Since joining the FTE/Custom synthesis team I have worked on a number of different projects for customers in a wide range of different industrial areas, such as the Pharmaceutical, Petrochemical, Agrochemical and Fine Chemical industries.

Q: What do you think is Key Organics' greatest strength?

A: The staff. It is not only the individuals experience and expertise but also the collaborative way in which we work that allows us to complete challenging projects by drawing on one another's strengths.

Key Organics

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For more information, please contact us at:

Key Organics Ltd.,
Highfield Road Industrial Estate,
Camelford,
Cornwall PL32 9RA,
UK

T: +44 (0)1840 212137
F: +44 (0)1840 213712
E: enquiries@keyorganics.net

Key Organics Inc.,
Suite 100,
55 North Road,
Bedford,
MA 01730

Toll Free No: 855 808-2700
Or: 781 280-5000
E: enquiries@keyorganics.net

www.keyorganics.net

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