Issue 5 | January 2014

Key Organics Newsletter

Chemistry | Innovation | Quality

Key Organics would like to wish all its Newsletter readers a Happy New Year! We begin 2014 with news of our new alliance with Almac who have appointed Key Organics as their exclusive and global partner for marketing their entire catalogue collection of R&D compounds. With next day delivery and assured quality, the Almac product portfolio is now available alongside our fast growing BIONET product range.

Within our technology section, we profile two areas; (i) the supply of bespoke reference standards for agrochemical metabolites and manufacturing impurities and (ii) the synthesis of (*S*)-2,6-dimethyltyrosine by catalytic asymmetric hydrogenation. We interview Jody Ali, our recently appointed New Product Development Manager and also profile our Q1 event attendance; we hope to meet you at one soon!

BIONET | On track to build a collection of over 100,000 niche R&D compounds!

Building a high value and niche collection of R&D products continues to be the primary objective for our BIONET product range, with a current inventory of 74,000 products many of which are unique to Key Organics. During 2013 we increased our BIONET collection by over 9,000 new compounds from both in-house activities and a number of new strategic alliances with partners who have the same high quality approach and can meet follow-through needs for scale-up and late-stage development. Our plans are now focused on further building an on-site inventory to over 100,000 (*Figure 1*) compounds by the end of 2015 but maintaining the same values and customer benefits that are consistent with our BIONET brand (*Table 1*).

Figure 1.
Recent growth & planned targets for BIONET

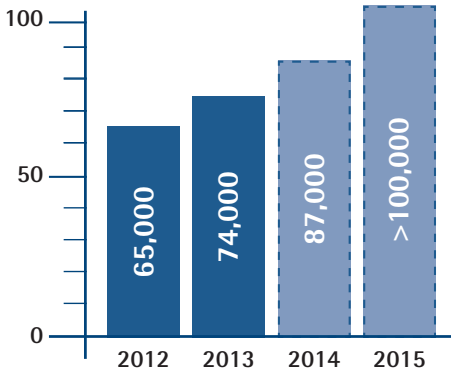


Table 1.
BIONET customer benefits

New & Novel Compounds:
- Intermediates
- Fragments
- Screening
- Biochemicals

Guaranteed Quality:
- >95% Purity
- Full CoA

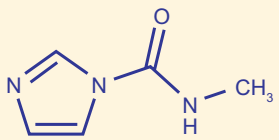
Reliability:
- Next day delivery
- Assured quality
- Full technical support
- >95% in stock

Our new alliance with Almac

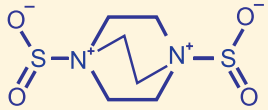
provides an example of our successful co-marketing partnership model and complements other deals that we announced in 2013 with Pareon Chemicals Ltd and Advanced Molecular Technologies Pty Ltd. Key Organics will stock and market the entire range of Almac products within our BIONET product group for worldwide 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**

New reagents now available from BIONET



GH-0723
N-methyl-*1H*-imidazole-1-carboxamide
CAS Number 72002-25-6



LH-0733
1,4-Diazabicyclo[2.2.2]octane-1,4-diium -1,4-disulfinate (DABSO)
CAS Number 119752-83-9

_N_-Methyl carbamoylimidazole (GH-0723) is our new methylisocyanate equivalent that offers a safer approach over current methodology and is now available in R&D quantities. The non-availability of methyl isocyanate on laboratory scale restricts access to methyl ureas, methyl carbamates and methyl thiocarbamates. As a safe methyl isocyanate equivalent, *N*-methyl carbamoylimidazole provides the synthetic organic chemist ready access to these essential functional groups.

DABSO (LH-0733) has been demonstrated as a sulfur dioxide alternative in various applications such as with Grignard reagents to form sulfinates, which can then be converted *in situ* to sulphonamides. In addition, with anilines and iodine sufonylureas can be readily formed.

For more information please see our information sheet available at:
www.keyorganics.net

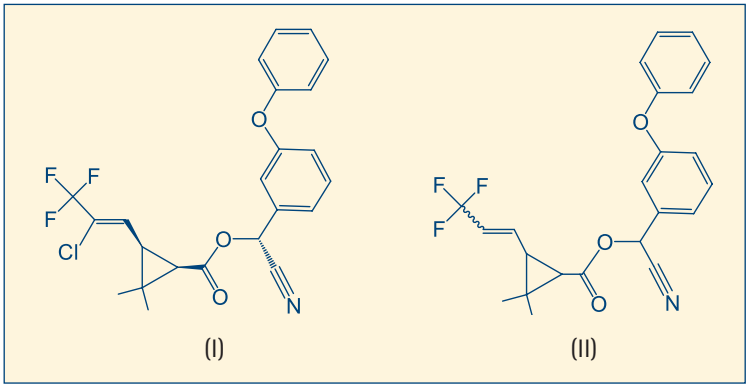
Key Organics
Chemistry Services

Custom Synthesis Case Study – Agrochemical Manufacturing Impurities

In conjunction with our longstanding expertise in the supply of BIONET building blocks and screening compounds into the agrochemical sector, our Chemistry Services business has extensive experience in the supply of bespoke reference standards for agrochemical metabolites and manufacturing impurities on a custom synthesis basis.

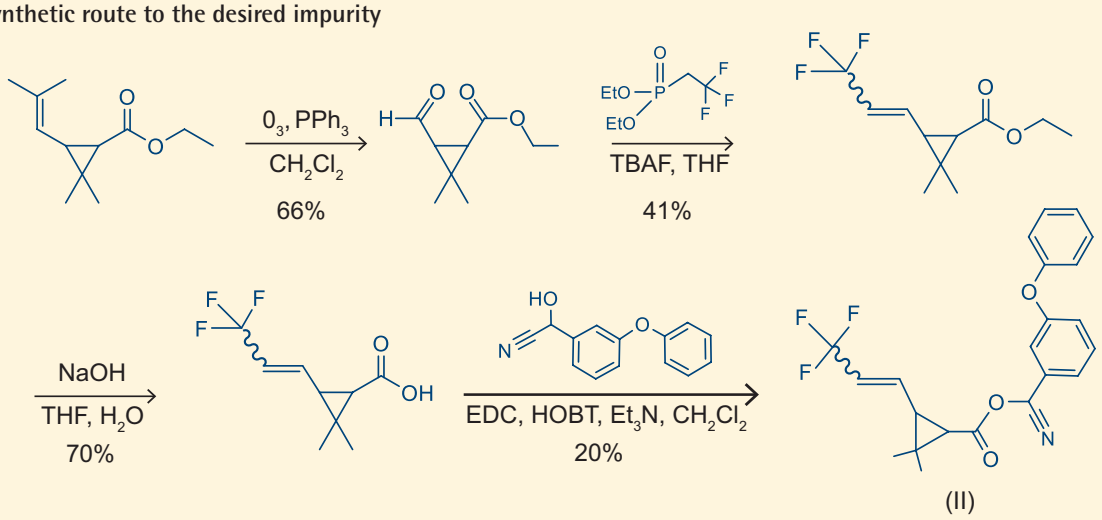
Lambda-cyhalothrin (I; CAS 91465-08-6) is a synthetic pyrethroid insecticide that mimics the structure and insecticidal properties of the naturally-occurring insecticide pyrethrum which comes from the flowers of chrysanthemums. It is commercially produced as a mixture of two of the four enantiomers (i.e. the *cis* 1*R*α*S* enantiomeric pair) of cyhalothin. Synthetic pyrethroids, like lambda-cyhalothrin, are often preferred as an active ingredient in insecticides because they remain effective for longer periods of time. It is a colorless solid, although samples can appear beige, with a mild odor. The compound has low water solubility, is nonvolatile and is used to control insects in cotton crops.

As part of the regulatory process for a new pesticide filling, one of our customers has recently required a sample of (cyano-3-phenoxybenzyl-2,2-dimethyl-3-[3,3,3-trifluoroprop-1-en-1-yl]cyclopropane-1-carboxylate)-(II), a proposed manufacturing impurity of lambda-cyhalothrin which arises from a feedstock impurity.



The synthesis route employed for the production of the analytical standard is summarised in *Scheme 1*. Ethyl chrysanthemumate was subject to ozonyltic cleavage to produce ethyl 3-formyl-2,2-dimethylcyclopropane-1-carboxylate[1] which was then converted to ethyl 2,2-dimethyl-3-[3,3,3-trifluoroprop-1-en-1-yl]cyclopropane-1-carboxylate via Horner-Wadsworth-Emmons olefination with (2,2,2-trifluoroethyl)triphenylphosphonium trifluromethanesulfonate[2]. Following ester saponification, esterification with the cyanohydrin derived from 3-phenoxybenzaldehyde affords the proposed impurity (II) as an isomeric mixture.

Scheme 1. Synthetic route to the desired impurity



Although the standard produced correlated with the observed impurity in the technical grade material, it became apparent that the pesticide impurity consisted of only one of the possible diastereomers of (II). In order to proceed with the filling, the regulator required both identification of the relative stereochemistry of the impurity, and confirmation that our standard contained this possible isomer.

In addition, we undertook additional consultancy work for this client that involved a rigorous review of the manufacturer's synthesis route and demonstrated with high probability the likely relative stereochemistry of the observed impurity. Coupled with a reasoned assessment of the stereochemical outcome of the above described synthetic transformations, we were able to satisfy the regulator that our mixed isomer sample contained the single impurity diastereomer and assist this client in obtaining regulatory approval for their material.

Other recent examples of pesticides for which we have produced impurities as reference standards for the regulatory process include (but not limited to): cymoxanil, difenoconazole, esfenvalerate, fludioxonil, fluometruron, fluroxypyr-meptyl, iprodione, metazachlor, oxasulfuron, oxyfluorfen, propamocarb, propyzamide, pyriproxyfen, tebuconazole, terbuthylazine and thidiazuron.

Please contact us for more information at: enquiries@keyorganics.net
Our Agrimediates collection can be found at: www.keyorganics.net

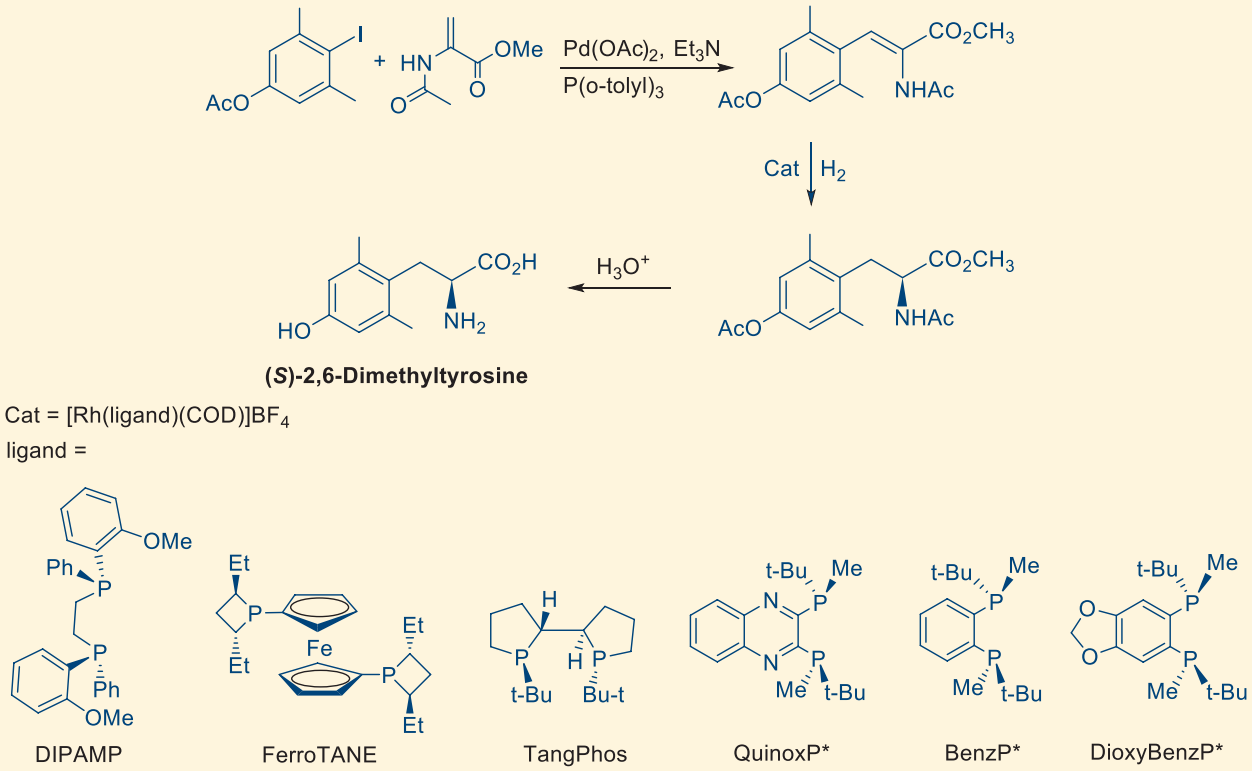
[1] M. Qi, J. Zhou, Y. Youfa, S. He and D. Zhang, US2012076846
[2] T. Hanamoto, N. Morita and K. Shindo, *Eur. J. Org. Chem.*, 2003, 4279-4285

Ligand Selectivity in the Asymmetric Synthesis of (*S*)-2,6-Dimethyltyrosine

(*S*)-2,6-Dimethyltyrosine is an unnatural amino acid that is used in the synthesis of the δ-opioid antagonist, Dmt-Tic pharmacophore[1] and several other pre-clinical development candidates. Reported literature approaches involve the catalytic asymmetric hydrogenation of the pro-chiral dehydroaminoacid substrate; (*Z*)-2-acetamido-3-(4-acetoxy-2,6-dimethylphenyl)-prop-2-enoate that can be readily prepared at scale (*Scheme 2*).

There are several reported asymmetric hydrogenations that all utilise different chiral bisphosphine ligands within their respective [Rh(chiral bisphosphine)(1,5-COD)]BF_4 catalysts. The ligands range from (*R,R*)-DIPAMP (Beck[2]) to (*S,S*)-Et-FerroTANE (Praquin[3]), (*R,R,S,S*)-TangPhos (Lennon[4]), QuinoxP* (Imamoto[5]), BenzP* (Imamoto), and DioxyBenzP* (Imamoto) that and are shown in Scheme 2.

Scheme 2. Synthesis of (*S*)-2,6-dimethyltyrosine by catalytic asymmetric hydrogenation



With the Imamoto ligands, optimal results were obtained using dichloromethane at room temperature and 20 atm. Optical purities (e.e) with the rhodium catalyst derived from DioxyBenzP* provided the desired product in 98.2% e.e., BenzP* was similarly high at 98.7% e.e. and QuinoxP* achieved 99.2% e.e.(*Table 2*). Lowering the catalyst loading to 0.1 mol % also enabled full conversion into the product without any decrease of the enantioselectivity.

We note that Praquin and co-workers abandoned the use of (*R,R*)-DIPAMP and instead resorted to FerroTANE and that this approach afforded the product in 93% e.e.. Significantly, the S/C ratio could be improved five-fold to 500:1 compared with the equivalent DIPAMP system and reaction completion was still observed within an acceptable timescale and without any loss in enantiomeric purity. The Rh catalyst derived from TangPhos has been reported to proceed with higher S/C ratios, presumably because it is optimised relative the other systems (*Table 2*).

Table 2. Variables in the Catalytic Asymmetric Synthesis of (*S*)-2,6-dimethyltyrosine

Ligand	S/C	Solvent	P (atm)	T (°C)	(h)	(e.e)	Ref'
(*S,S*)-DioxyBenzP*	200	CH_2Cl_2	20	r.t.	18	98.2	5
(*S,S*)-BenzP*	200	CH_2Cl_2	20	r.t.	18	98.7	5
(*S,S*)-QuinoxP*	200	CH_2Cl_2	20	r.t.	18	99.2	5
(*R,R*)-DIPAMP	100	AcOEt	5	60	24	92.0	2
(*S,S*)-FerroTANE	500	AcOEt	5	60	16	93.0	3
(*R,R,S,S*)-TangPhos	2,000	MeOH	15	30	-	98.0	4

(*S*)-2,6-dimethyltyrosine HCl salt and other analogues are available commercially in gram and multi-Kg quantities from Key Organics.

[1] Y. Sasaki and A. Ambo, *International Journal of Medicinal Chemistry*, Vol. 2012 (2012), Article ID 498901.
[2] J.H. Dygos, E. Yonan, M.G. Scaros, O.J. Goodmonson, D.P. Getman, R.A. Periana and G.R. Beck G.R., *Synthesis*, 741-743, (1992).
[3] C.F.B. Praquin, P.D. de Koning, P.J. Peach, R.M. Howard, and S.L. Spencer, *Org. Process Res. Dev*, Vol. 15, 1124-1129, (2011).
[4] I. Lennon, Presentation at Catalysis Development Conference, Newmarket, UK, (2013).
[5] T. Imamoto, Ken Tamura, Z. Zhang, Y. Horiuchi, M. Sugiya, K. Yoshida, A. Yanagisawa and I.D. Gridnev, *J. Am. Chem. Soc.*, Vol. 134, 1754–1769, (2012).

Upcoming Events:

21 – 24 January
InformEx 2014
Miami Beach, FL
www.informex.com/informex-usa

13 February
Chemistry Research Labs Exhibition
The University of Oxford
www.chem.ox.ac.uk

18 - 19 February
Discovery Chemistry Congress
Barcelona
http://selectbiosciences.com/conferences/index.aspx?conf=DCC2014

22 February
Life Sciences Scotland Conference & Partnering Event
Edinburgh, UK
www.lifescience2014.co.uk/conference/4580375817

6 March
Innovations In Healthcare
The University of Sheffield
http://ssg.sheffield.ac.uk/events/iih

6 - 7 March
BioWales
Millennium Centre, Cardiff
https://biowales.com/en/

10 - 12 March
Trade mission to Europe's Ag Chem Heartland
Switzerland and Germany
www.cia.org.uk/default.aspx

17 - 21 March
Bio Europe Spring
Turin, Italy
www.ebdgroup.com/bes/index.php

Staff Interview

with Jody Ali,
New Product Development Manager

Q: Please tell us a bit about yourself?

A: I grew up in Sheffield, before moving to Newquay at the age of thirteen. I studied at the University of Bath, obtaining a BSc (Hons) in Chemistry. After moving back to Cornwall in 1999, I gained employment as an Assistant Chemist with Key Organics. A few years later, I met Hannah, got married and started a family. The West Country is a beautiful part of the country to live in and a fantastic place to bring up our two young children. We particularly enjoy heading off for the day in our clapped-out old camper van. The kids seem to really enjoy the adventure! When we are not away camping or at the beach, I like painting, buying old junk, listening to music and I am a keen sports fan.

Q: What is your role within Key Organics?

A: The BIONET catalogue was launched shortly before my arrival and I was always heavily involved in a lot of the decisions that took place over the years. It was this involvement that led to me becoming the Deputy Head of Intermediates. My main focus was on the remake aspect of the department, making sure all items were restocked quickly with perfect quality. I have always been extremely passionate about this. Through everybody's hard work, we now have an enviable position of >95% in stock, which we offer with next day delivery and assured quality. This level of service is unique from a company of our size, and I am proud to have been part of this. More recently my focus has been on external collaborations and more unique new product offerings. So I was delighted when I was given the opportunity to undertake my new role of New Product Development Manager, which will allow me to grow our large and diverse collection further.

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

A: It has always been refreshing, that at Key we have actively been encouraged to pursue any avenue of Chemistry that we find interesting. This freedom to look at exciting new areas will continue and be expanded upon in my new role. I recently have had the pleasure of being involved with two new product launches. The first product is a safer alternative to methyl isocyanate (GH-0723) used for making methyl ureas, and the second is DABSO (LH-0733) which is a stable, safer and easy to handle reagent which can replace SO2 in organic synthesis.

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

A: The staff; their skills, hard work, professionalism and honesty.

Key Organics

Chemistry | Innovation | Quality

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New Satellite Offices, Let's Meet-up!

We are now able to meet with customers at our new satellite offices at BioCity Nottingham and BioCity Scotland. Of course everyone is still welcome to visit HQ in Cornwall!

Acknowledgements: *Design by* David Anthony, AK Design (Scotland) Ltd.