SYNSTORIES

- Featured SynStory: Synthetic Tubulysins as Super-Potent Warheads for Cancer Chemotherapy

- Construction of an All-Carbon Quaternary Stereocenter by the Peptide-Catalyzed Asymmetric Michael Addition of Nitromethane to β-Disubstituted α,β-Unsaturated Aldehydes

- Palladium-Catalyzed N-(2-Pyridyl)sulfonyl-Directed C(sp³)–H γ-Arylation of Amino Acid Derivatives

- One-Pot, Catalyst-Free Synthesis of β- and γ-Hydroxy Sulfides Using Diaryliodonium Salts and Microwave Irradiation

CONTACT

Your opinion about SYNFOM is welcome, please correspond if you like: marketing@thieme-chemistry.com
Dear readers,

Which aspects of your academic work do you like the most? The last two weeks were quite mixed and intense for me; normally I do not have much teaching (don’t tell it to my College though...) but in the last few days I had to mark a few exams and I dealt with some other teaching-related activity too. Then, I organized a one-day workshop with ca. 50 attendees. I have also been finalizing a grant application, drafting a couple of manuscripts, evaluated several grant applications and a couple of manuscripts, dealt with the usual supervision of my postgraduate students and postdocs. Then, I did quite a lot of ‘administration’ work connected with the fact that I am directing two research centers of my university. And obviously I took care of SYNFORM. Plus some other miscellaneous stuff. Luckily, I did not have to travel. But, unfortunately, I had very little time for keeping myself up-to-date with the literature, which is something that really annoys me. That’s because studying the literature and designing new experiments and projects is by far my favorite activity, I really love browsing journals online and getting inspiration and ideas for new research endeavors. I guess many of you will agree that this is what really makes our work special, together with the excitement of seeing our research plans materialized into exciting experimental results, expected or not (which sometimes is even better!). And I suspect this sentiment is also shared by the researchers whose work is featured in this new issue of SYNFORM, which includes the following SYNSTORIES: the Pd-catalyzed C—H γ-arylation of α-amino acids reported by J. C. Carretero (Spain); a novel stereoselective approach to all-carbon quaternary stereocenters catalyzed by peptides, discovered by K. Kudo (Japan); a novel synthetic approach to β- and γ-hydroxy sulfides developed by J. Leazer (USA); the FEATURED SYNSTORY on the highly potent toxic payloads for targeted chemotherapy developed by P. Lazzari and his company (Italy).

Enjoy your reading!

Matteo Zanda
Editor of SYNFORM

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CONTACT

If you have any questions or wish to send feedback, please write to Matteo Zanda at: Synform@chem.polimi.it
Amino acids are critically important molecules and key building blocks in a vast number of scientific areas spanning molecular sciences and biomedicine. Only 20 α-amino acids are coded for in the genetic code of humans and many amino acids are rare compounds, neither commercially available nor easily obtained by chemical synthesis. Over the last decade, Pd-catalyzed C(sp3)–H activation reactions have emerged as a powerful and atom-economical synthetic methodology. However, the application to the functionalization of remote C(sp3)–H bonds in organic synthesis is still at its early stages and significant advancements in this field are of much general interest for the chemical community. Particularly, the functionalization of α-amino acids through a Pd-catalyzed C(sp3)–H activation process is very challenging due to the importance of non-proteinogenic amino acids. However, few examples of functionalization of α-amino acid derivatives through a Pd-catalyzed C(sp3)–H activation process, especially regarding the remote α-functionalization process, are known.

The research group of Professor Juan Carlos Carretero at the Universidad Autonoma de Madrid (Spain) has developed an efficient methodology for the Pd-catalyzed γ-CH₂ arylation of simple α-amino acid esters with iodoarenes. Professor Carretero explained: “This process relies strongly on the use of the N-(2-pyridyl)sulfonyl moiety as a crucial activating and directing group. The synthetic utility of this protocol is demonstrated by the γ-arylation of a variety of N-(2-pyridyl)sulfonyamide α-amino acid derivatives (e.g., from valine, threonine or allo-isoleucine), including also α-quaternary amino acids and β-amino acids (Scheme 1).”

To highlight the synthetic utility of this process in non-proteinogenic amino acid synthesis, the overall three-step sequence for the γ-diarylation of L-valine ester, including the initial introduction and final removal of the directing group, has been achieved (Scheme 2). “From a synthetic point of view, it is important to note that practically no racemization at the Cα center was observed, neither in the Pd-catalyzed aryla-
tion reaction nor in the final cleavage of the sulfonyl moiety (98% ee),” said Professor Carretero.

As a challenging extension of the process, this Pd-catalyzed γ-CH$_3$ arylation is also effective in the functionalization of dipeptide substrates (Scheme 3). “As far as we are aware,” remarked Professor Carretero, “these are the first examples for the remote Pd-catalyzed γ-C(sp$^3$)–H functionalization of dipeptides.” He concluded, “We anticipate that the use of the directing 2-(pyridyl)sulfonyl moiety can open new perspectives in the field of metal-catalyzed direct functionalization of remote C(sp$^3$)–H bonds.”

**Scheme 2**

**Scheme 3**

**About the authors**

Juan Carlos Carretero received his PhD from the Universidad Autónoma de Madrid (UAM, Spain) in 1985 under the supervision of Professor José L. García Ruano. After postdoctoral studies (1985–1988) at the Université Catholique de Louvain (Belgium) with Professor Léon Ghosez, he joined the Department of Organic Chemistry of the UAM, where he became Associate Professor in 1988 and Professor of Organic Chemistry in 2000. In 2010 he received the Janssen-Cilag Award in Organic Chemistry from the Spanish Royal Society of Chemistry. He is currently head of the Department of Organic Chemistry (UAM). His research interests are focused on the development of novel processes in asymmetric catalysis, stereocontrolled metal-catalyzed reactions and C–H activation processes.

M. Ángeles Fernández-Ibáñez received her PhD degree from Universidad Autónoma de Madrid (UAM, Spain) in 2006 under the supervision of Professor José L. García Ruano. During this period, she had a postdoctoral stay in Boston College (USA).
Jose Antonio Romero Revilla was born in Madrid (Spain) in 1985. He studied at the Universidad Complutense de Madrid (Spain) and received his BSc in 2008. Subsequently, he worked at Consejo Superior de Investigaciones Científicas (CSIC, Spain) under the supervision of Dr. Francisco Sánchez until 2010 when he joined the group of Juan C. Carretero at UAM where he is currently doing his PhD.

Nuria Rodríguez was born in 1978 in Valencia (Spain). After completion of her chemistry studies at the University of Valencia (Spain), she gained her doctorate in the group of Professor Gregorio Asensio and Dr. Mercedes Medio-Simón. She worked with Lukas J. Gooßen as a Humboldt postdoctoral fellow starting in 2006. The emphasis of her work was the development of decarboxylative cross-coupling reactions. In 2011, she took up a Ramon y Cajal research position at UAM with Juan C. Carretero. Her current research focuses on the development of catalytic systems for the activation of inert C–H bonds.
Mimicking the synthetic efficiency, specificity, stereocontrol and environmental sustainability of enzymes is a stimulating challenge for synthetic organic chemists. Recently, the group of Professor Kazuaki Kudo from The University of Tokyo (Japan) developed a process for installing synthetically challenging quaternary carbon centers in a stereocontrolled manner using a peptide-based catalytic system that closely simulates many peculiar aspects of enzymatic catalysis.

In fact, Professor Kudo and co-worker Dr. Kengo Akagawa have developed resin-immobilized asymmetric peptide catalysts having secondary structures that work under aqueous conditions. Professor Kudo said: “A representative example is Pro-Ω-Pro-Aib-Trp-Trp-(Leu)2 bound to amphiphilic PEG-PS resin (Aib = 2-aminoisobutyric acid).” He continued: “The pentapeptide at the N-terminus adopts a turn structure whereas the polyleucine part has an α-helical structure. This catalyst was designed to mimic enzymes as follows: 1) enzymes have higher-order structures that are suitable for catalytic functions, and 2) they are amphiphilic molecules with a hydrophobic microenvironment at the reaction center, hence smoothly catalyze reactions in water.” The catalyst was effective for asymmetric hydride-transfer reactions to α,β-unsaturated aldehydes (Org. Lett. 2008, 10, 2035; Tetrahedron: Asymmetry 2009, 20, 461), asymmetric Friedel-Crafts-type reactions to α,β-unsaturated aldehydes (Tetrahedron Lett. 2009, 50, 5602; Adv. Synth. Catal. 2012, 354, 1280), and asymmetric α-oxamination of aldehydes (Chem. Commun. 2010, 46, 8040; Org. Lett. 2010, 12, 1804; Org. Lett. 2011, 13, 3498).

While exploring the potential of this peptide catalyst, Dr. Akagawa found that asymmetric addition of nitromethane to β-disubstituted-α,β-unsaturated aldehydes occurred smoothly. The amine-catalyzed asymmetric addition of nitromethane to β-monosubstituted-α,β-unsaturated aldehydes through an iminium-ion activation mechanism is a well-known reaction. However, that with β-disubstituted analogues has not been reported previously. “This might be due to the steric congestion at the β-position which lowers the reactivity for 1,4-addition and allows competing side reactions including 1,2-addition of nitronate anions to occur,” said Professor Kudo, who further remarked: “In fact, the reactions with several known secondary amine catalysts resulted in the formation of a complex mixture in which only a small amount of 1,4-adduct was included.

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After considerable tuning of the reaction conditions and the catalyst, we were able to show the generality of this reaction for a range of substrates.”

Professor Kudo continued: “We think the key to the realization of this reaction might be due to the successful construction of the hydrophobic microenvironment in aqueous solvents with this catalyst. Use of a protic solvent system might also play an important role in lowering the concentration of reactive ionic species that are relevant to side reactions.”

It should be emphasized that the products could be easily transformed to β,β-disubstituted-γ-aminobutyric acids, which should be of interest from a pharmacological point of view due to the structural relationship with GABA, an inhibitory neurotransmitter.

“I feel that we have unveiled only a small part of the rich world of peptide catalysts,” concluded Professor Kudo. “We are now trying to find more ‘enzyme-like’ peptide catalysts that show high regio- or chemoselectivity which cannot be attained by small-molecule catalysts.”
Aromatic β- and γ-hydroxy sulfides are valuable organic compounds that have been used in the construction of important biologically active compounds, natural products, organolithium complexes, metallophthalocyanines, α,β-unsaturated lactones and organic intermediates, such as aryl vinyl sulfones, to name a few. The C–S cross-coupling reaction is a versatile organic transformation that finds applications in various organic, pharmaceutical and material chemistry synthesis and manipulations. A C–S bond-formation reaction that does not make use of transition metals and expensive ligands would be highly desirable from both the environmental and synthetic viewpoints. With this idea in mind, Dr. Buchi Reddy Vaddula, Dr. Rajender Varma and Dr. John Leazer at the US Environmental Protection Agency (Cincinnati, OH, USA) decided to develop an efficient and simple protocol for the synthesis of hydroxy sulfides. General routes for their preparation usually involve the nucleophilic ring opening of epoxides with thiols. Dr. Vaddula said: “Our ongoing exploratory studies on the application of hypervalent iodine reagents led us to an efficient synthesis of β- and γ-hydroxy sulfides using readily available reagents. This eco-friendly protocol enables the construction of various important organic intermediates and bioactive and natural products from simple and readily accessible starting materials and is amenable to the assembly of a library of β- and γ-hydroxy sulfides.”

Dr. Vaddula continued: “We devised a novel strategy for the one-pot, catalyst-free synthesis of β- and γ-hydroxy sulfides.” This approach to hydroxy sulfide synthesis involves a three-component reaction of diaryliodonium salts, potassium thiocyanate, and 1,2- or 1,3-diols such as ethylene glycol and propane-1,3-diol. “We deem diaryliodonium salts as an efficient substitution for aryl halides in arylation reactions, due to the electrophilic nature of the iodonium salt harnessed by the good leaving ability of one of its arene ligands in the form of iodoarene,” said Dr. Vaddula. “The simplest preparation of diaryliodonium salts, in turn, needs only arenes, elemental iodine, and mild reaction conditions,” he added.

The investigations by the Ohio-based researchers revealed that the three-component reaction progressed via the intermediate formation of an aryl thiocyanate within 10–25 minutes. However, interestingly, an independent reaction of aryl thiocyanate with diol under the same conditions failed to yield the desired product. Another feature is that, in the case of diols containing primary and secondary alcohols, this one-pot reaction acts preferentially on primary alcohols over secondary alcohols. This protocol seems inapplicable for 1,4-diols, leading to speculation that a hydroxyl group in the neighborhood (within a three-carbon distance) helps in assisting the thionation reaction.

“The literature reports the preparation of hydroxy sulfides by heating aryl thiocyanates with ethylene glycol in the presence of triphenylphosphane, which generates its oxide as the byproduct that is detrimental to the environment,” said Dr. Vaddula. “Keeping in mind the importance of these products
in organic and medicinal chemistry and adhering to the tenets of green chemistry, this protocol assumes special significance,” he continued. “We strongly believe that a sustainable method that avoids the deployment of additional reagents and circumvents isolation steps for intermediates is therefore highly desirable and paves the way for further explorations of this newer strategy,” Dr. Vaddula concluded.

About the authors

Buchi Reddy Vaddula was born in India and received his Bachelors and Masters in Pharmacy from Birla Institute for Technology and Science (BITS, Pilani, India). He received his PhD under the supervision of Professor D. Kumar from the same institution. He has worked on multicomponent reactions in the synthesis of bioactive compounds. Currently, he is working as an ORISE postdoctoral fellow, researching on greener synthetic methods for bioactive compounds and nano catalysis with Professor R. S. Varma and Dr. J. Leazer at US EPA, Cincinnati (OH, USA).

Rajender S. Varma was born in India and obtained his PhD in 1976. After postdoctoral research at the Robert Robinson Laboratories, Liverpool (UK), he was a faculty member at Baylor College of Medicine and Sam Houston State University (USA) prior to joining the Sustainable Technology Division at US EPA in 1999. He has over 40 years of research experience in management of multi-disciplinary technical programs ranging from natural products chemistry to therapeutics and development of environmentally friendlier alternatives for synthetic methods, using microwaves, ultrasound, etc. Lately, he has focused on greener approaches to assembly of nano materials and sustainable applications of magnetically retrievable nano catalysts in benign media. He has published over 350 scientific papers and has been awarded 12 US patents.

John Leazer obtained his BSc from Davidson College (NC, USA), his MSc in synthetic organic chemistry from the North Carolina State University (USA) and his PhD in synthetic organic chemistry from the University of Pennsylvania (USA). After completing his graduate studies, John joined Merck, where he worked as a process chemist for 22 years. He is the Director of the Sustainable Technology Division in the US EPA’s Office of Research and Development and has responsibility for the division’s research portfolio and sustainability advances.
Tubulysins are a family of natural tetrapeptides produced in small quantities (<4 mg·L⁻¹ culture broth) by two different species of Myxobacteria.¹ Tubulysins are extremely toxic to mammalian cells, with IC₅₀ values in the range of 0.01–10 nM.² The cytotoxic activity of the tubulysins is due to their ability to bind tubulin and disintegrate microtubules of dividing cells, thus inducing apoptosis.³ Owing to their remarkable interest and great potential as potent anticancer agents, several total syntheses of natural or modified tubulysins have been published.⁴

Structurally, tubulysins are linear tetrapeptides incorporating L-isoleucine and three unnatural amino acids. At the N-terminus, all the family members have N-methyl pipecolic acid (Mep) and isoleucine (Ile). The unusual amino acid tubuvaline (Tuv) containing a thiazole heterocycle occupies the central position. At the C-terminus there is either tubuphenylalanine (Tup, present in tubulysin D and others) or tubutyrosine (Tut, present in tubulysins A and others), which are γ-amino acid homologues of phenylalanine and tyrosine, respectively. Additionally, the N-terminal moiety of Tuv may be further functionalized with an unusual N,O-acetal substituent having different ester functionalities, which is of paramount import-

<table>
<thead>
<tr>
<th>Compound</th>
<th>IC₅₀ (nM) on Different Cell Lines</th>
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<tbody>
<tr>
<td></td>
<td>MESO (48 h)</td>
</tr>
<tr>
<td>KEMTUB010</td>
<td>0.5</td>
</tr>
<tr>
<td>TUBULYSIN A</td>
<td>5.120</td>
</tr>
<tr>
<td>PACLITAXEL</td>
<td>26</td>
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<tr>
<td>VINBLASTIN</td>
<td>21.5</td>
</tr>
<tr>
<td>DOXORUBICIN</td>
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MESO = Malignant peritoneal mesothelioma cell line; STO = Mouse embryonic fibroblast cell line; LoVo = Human colon carcinoma cell line; LoVo/DX = Doxorubicin-resistant Human colon carcinoma cell line; MCF7 = Breast cancer cell line; MCF7/Dx = Doxorubicin-resistant Breast cancer cell line.
ance for imparting the high potency typical of most cytotoxic natural tubulysins, such as A and D.

Paolo Lazzari and co-workers at KemoTech (www.kemotech.it) have recently developed a scalable synthesis (up to one gram) of super-potent synthetic analogues of the natural tubulysins.1 KemoTech’s proprietary synthetic tubulysins have distinctive features, such as (1) increased potency and cytotoxicity on a number of cancer cell lines, including multidrug-resistant cell lines (see Table) and (2) increased metabolic and chemical stability relative to the natural tubulysins, such as tubulysins A and D. In fact, KemoTech’s proprietary tubulysins feature a highly stable alkylaryl, alkylcycloalkyl, alkylheteroaryl, etc. group R2 replacing the labile and synthetically challenging alkoxy carbonylalkyl N-Tuv fragment which characterizes the natural tubulysins.

Owing to their impressive cytotoxicity, synthetic tubulysins appear to be ideal candidates for targeted chemotherapy. Therefore these compounds have been successfully functionalized with different chemical handles for allowing the attachment to targeting vectors, such as antibody formats,2 peptides, polymers and nanoparticles. However, synthetic tubulysins also have a remarkable potential as ‘classical’ anticancer drugs, as demonstrated by very encouraging preliminary preclinical results showing an interesting therapeutic window despite the extremely high potency featured by these tubulysin derivatives.

In summary, synthetic tubulysins are highly promising candidate drugs for oncology that may find important applications both as highly toxic payloads in targeted chemotherapy and as cytotoxic anti-cancer drugs, especially if a suitable therapeutic window can be identified.

**REFERENCES**

In the next issues:

SYNSTORIES

- Copper/Titanium Catalysis Forms Fully Substituted Carbon Centers from the Direct Coupling of Acyclic Ketones, Amines, and Alkynes (Focus on an article from the current literature)
- Phosphine-Based Redox Catalysis in the Direct Traceless Staudinger Ligation of Carboxylic Acids and Azides (Focus on an article from the current literature)
- Taming of Fluoroform: Direct Nucleophilic Trifluoromethylation of Si, B, S, and C Centers (Focus on an article from the current literature)

FURTHER HIGHLIGHTS

SYNTHESIS

Review on: Guanidine Organocatalysis (by P. Selig)

SYNLETT

Account on: Recent Progress in Chemistry of Mucohalic Acids: Versatile Building Blocks in Organic Synthesis (by J. Zhang et al.)

SYNFACS

Synfact of the Month in category “Synthesis of Heterocycles”: Synthesis of 3-Nitroindoles via an Intramolecular α-Selective Heck Reaction

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Homepage: www.thieme-chemistry.com

Publication Information
SYNFORM will be published 12 times in 2013 by Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany, and is an additional online service for SYNTHESIS, SYNLETT and SYNFACTS.

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