Hans-Dieter Arndt, Organic Chem Curr Res 2019, Volume 8
DOI: 10.4172/2161-0401-C1-030

10th European Organic Chemistry Congress

March 21-22, 2019 | Rome, Italy

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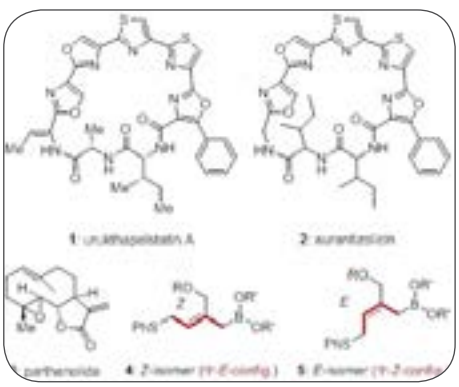
Total synthesis and functional studies of parthenolides and urukthapelstatins

The total synthesis of natural products is an important enabling step toward dedicated mode of action studies. Two case studies from our laboratory will be presented in the lecture. We have recently reported on an efficient total synthesis of the potent cytotoxin urukthapelstatin A. This synthesis utilizes a combination of thiolactonization and aza-Wittig ring contraction reactions to obtain high yields of the strained macrocycle. By using this technology structural variations are easily implemented. X-ray structures and biological activities will be presented. Based on these findings, the chemistry workflow was adapted and transferred to solid phase. The efficiency of this new methodology is demonstrated by the swift first total synthesis of aurantizolicin, a cryptic metabolite from *Streptomyces aurantiacus*. Structure and stereochemistry of the scarce natural product has thereby been unambiguously assigned. Progress toward studying the bioactivity and mode-of action of these polyazole cyclopeptides will be discussed. On the other hand, many methylene γ-lactone terpenes feature remarkable anti-inflammatory and neuritogenic activity. In this regard, the germacrane sesquiterpene parthenolide form the medicinal plant feverfew (*Tanacetum parthenium*) caught our interest. While semisynthetic approaches to and non-selective syntheses of this highly active natural product have been reported, incomplete access to stereoisomers and to derivatives has impeded medicinal chemistry and mode of action studies. Here, we will present the first stereoselective total synthesis of parthenolide that enables access to all its possible stereoisomers as well. It employs novel trisubstituted allylborane reagents that exert excellent stereocontrol as well as an efficient ring closure (80% yields) of the peculiar 10-membered ring scaffold.



Recent Publications

1. Schwenk S, Ronco C, Oberheide A, Arndt HD (2016). Eur. J. Org. Chem. 2016: 4795-99.
2. Oberheide A, Schwenk S, Ronco C, Semmrau LM, Görls H, Arndt HD (2018). Submitted.
3. Skinnider MA, Johnston CW, Edgar RE, Dejong CA, Merwin NJ, Rees PN, Magarvey NA (2018). Proc. Natl. Acad. Sci USA 113: E6343-51.
4. Oberheide A, Pflanze S, Stallforth P, Arndt HD (2018). In preparation.
5. Ghantous A, Sinjab A, Herceq Z, Darwiche N (2013). Drug Discov. Today 18:894-905.

Biography

Hans-Dieter Arndt is an enthusiastic synthetic organic chemist with expertise in medicinal chemistry and chemical biology. He studied chemistry at the universities of Ulm, Marburg, Germany, and Imperial College, London, UK. He has obtained his PhD degree in 2002 at Humboldt-University, Berlin, Germany. After postdoctoral research at CalTech, Pasadena, USA, he launched his independent career at the Max-Planck-Institute of Molecular Physiology, Dortmund, Germany. In 2011, he moved to Friedrich-Schiller University, Jena, Germany, where he currently holds the Chair of Organic Chemistry. He is the Director of the Institute of Organic and Macromolecular Chemistry and currently he is serving as Vice-Dean. His research interests include natural product synthesis, synthesis design, method development, and Chemical Biology and Chemical Ecology research.

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