Total Synthesis of Aurantoside G, an *N*-β-Glycosylated 3-Oligoenoyltetramic Acid from *Theonella swinhoei*

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3-Acyltetramic acids are metabolites of a variety of marine and terrestrial species such as sponges, bacteria, fungi, and lichens with an impressive range of biological and pharmacological activities. "This, and the scurrility that compounds with such deceptively 'simple' looking structures can turn out to be a nightmare when it comes to purification or spectral interpretation, has attracted the interest of synthetic organic chemists," said Professor Rainer Schobert from the University of Bayreuth (Germany). "Our group got involved with these compounds some twenty years ago when we serendipitously found a new Wittig-based access to their pyrrolidine-2,4-dione core. Since then we have learned the hard way that each structural subclass of 3-acyltetramic acids requires its own synthetic approach."

Professor Schobert explained: "When we focus on derivatives of marine origin there are, for example, the chemically robust melophlins, metabolites of bacteria that dwell on the sponge *Melophlus sarassinorum*, which can be readily synthesized by an acylation of the parent pyrrolidine-2,4-dione with the respective carboxylic acid chloride in the presence of an excess of $BF_3{\cdot}OEt_2$ according to a method by Raymond Jones.[1]" He continued: "In contrast, epicoccamide D, which is produced by the fungus *Epicoccum purpurascens* associated with the jellyfish *Aurelia aurita*, and which is comprised not only of polyketide and amino acid as all 3-acyltetramic acids, but also of a mannose, would not stand being steeped in Lewis acid. Its side chain had to be installed by other means prior to ring closure via a Dieckmann condensation as the final step (Figure 1).[2]"

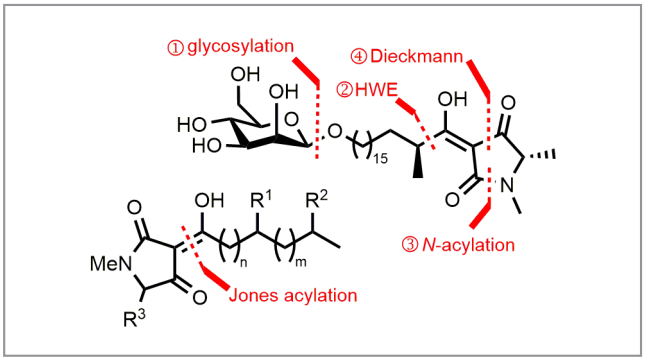


Figure 1 Synthetic access to melophlins (bottom/left) and epicoccamide D (top/right)

The genuine sponge metabolite aurantoside G posed even more intricate problems. "It is a deep-red solid which confers this color to the sponge (Figure 2, right, shows a protected derivative of the same color) and it is moderately active against *Candida albicans*.[3] This antifungal activity depends on the β-linkage between tetramic acid and sugar," explained Professor Schobert, continuing: "Given that aurantoside G is a natural product it is amazingly sensitive, and so are its components. Its chlorinated, highly unsaturated side chain is sensitive to light and prone to decomposition. Figure 2 shows a flask with its golden thioester which was built up by consecutive Wittig and HWE olefinations as planned by Sebastian Loscher and Markus Petermichl as early as in 2014."

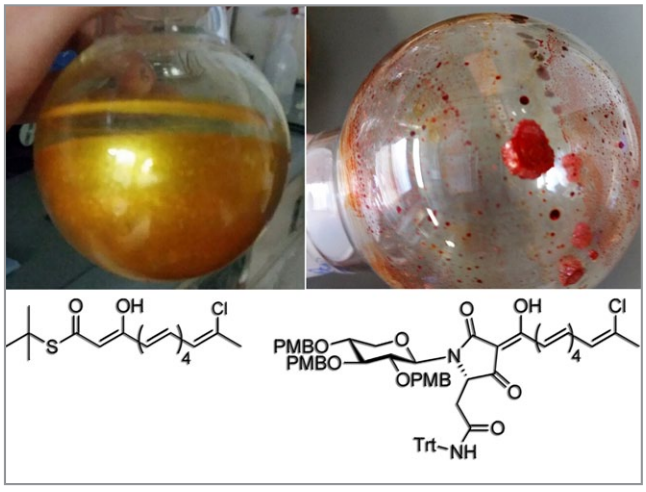


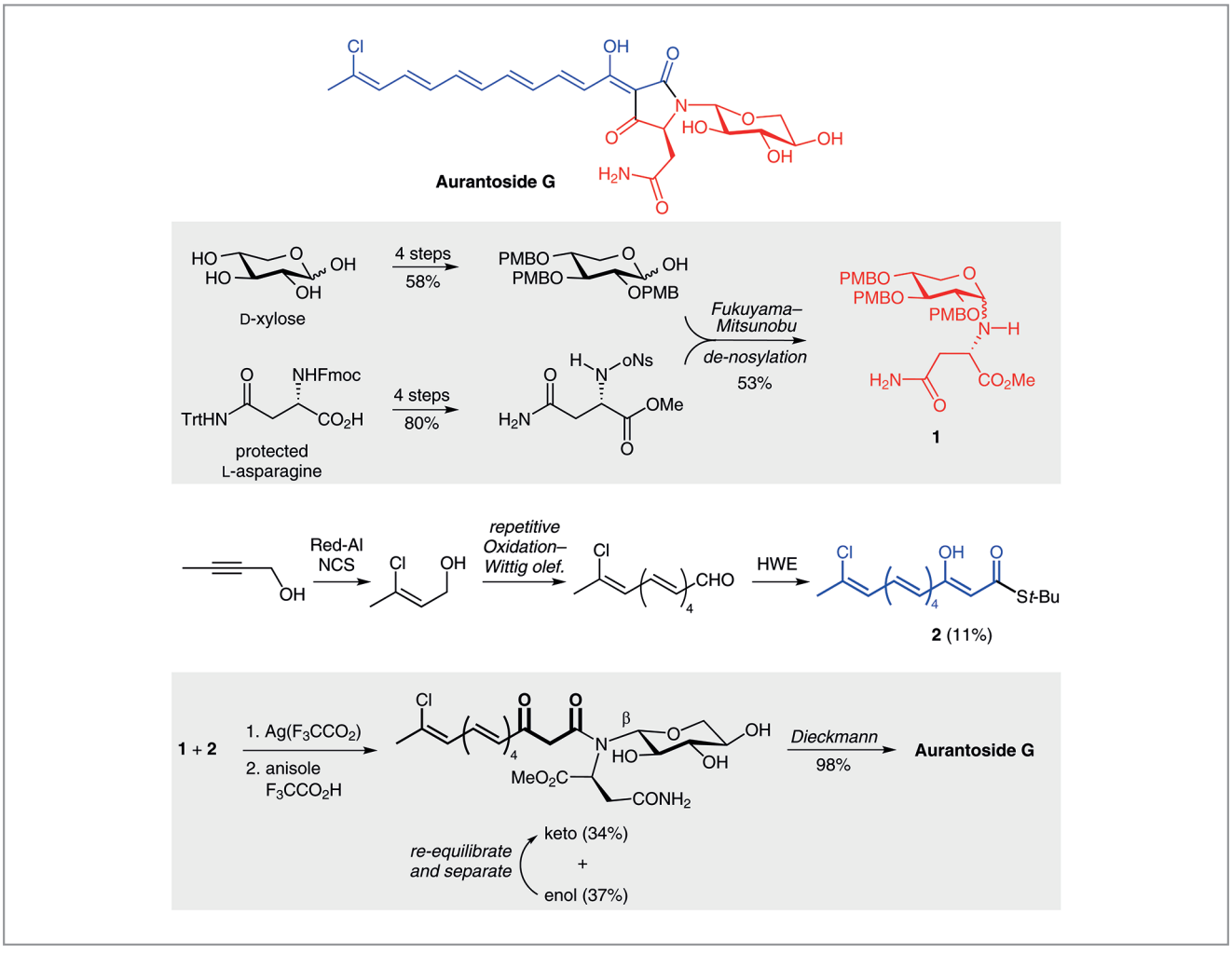
Figure 2 Flamboyant chemistry: the side-chain thioester (left) and a protected aurantoside G (right)

Professor Schobert recalls that Sebastian Loscher, who was then nearing the end of his PhD project, and Markus Petermichl, at that time embarking on his MSc project, also explored ways to attach a sugar to the nitrogen of a model 3-acyltetramic acid, but found it was not practicable. More successful were attempts to attach a protected xylose to an *N*-nosylated alanine ester via a Fukuyama–Mitsunobu reaction.

Professor Schobert said: "In the end, it took Markus a year and a half in the lab to synthesize aurantoside G by starting out on the basis of these exploratory experiments and circumventing a host of unforeseeable problems cropping up at almost every step."

Scheme 1 outlines the synthetic route that was eventually worked out. "Markus first attached the D-xylose to the asparagine by a Fukuyama–Mitsunobu reaction, which requires the nitrogen to be nosylated in order to render its hydrogen atom acidic enough," said Professor Schobert. "The actual glycosylation of this relatively electron-poor nitrogen atom was then possible only with electron-releasing *p*-methoxybenzyl (PMB) protecting groups on the sugar, as Markus and Sebastian had found out during their exploratory studies with alanine esters."

The resulting *N*-nosyl-*N*-xylosylasparaginate was de-nosylated to give building block **1** (red). This had to be *N*-acylated with the thioester **2** shown in Figure 2. "This thioester was synthesized in 11% yield over nine steps starting from (*Z*)-3-chlorobut-2-en-1-ol, which was prepared by reaction of but-2-yn-1-ol with Red-Al and *N*-chlorosuccinimide (NCS)," said Professor Schobert, who continued: "The stepwise chain elongation of this alcohol, by employing three cycles of domino oxidation–Wittig olefination using MnO_2 and $Ph_3P{=}CHCO_2Et$ followed by reduction of the product esters with DIBAL-H, afforded a pentenal. Due to its instability, it was immediately subjected to a HWE reaction with Steve Ley's *S*-*tert*-butyl 4-(diethylphosphono)-3-oxobutanethioate[4] to give the desired thioester **2**."



Scheme 1 Synthetic route to aurantoside G

The aminolysis of thioester **2** with a mixture of anomers of methyl *N*-D-xylosylasparaginate **1** and silver trifluoroacetate according to Ley's general protocol[5] afforded the corresponding β-keto amide (not shown in Scheme 1) as a pure β-isomer in 49% yield with respect to recovered, unreacted **1**. "Apparently, only the β-anomer of **1** enters into a reaction with **2**, due to the directing effects of the PMB groups. The recovered α-anomer was re-epimerized during workup," said Professor Schobert, who revealed that it took several cycles to convert the entire **1** into the β-keto amide. Cleavage of its PMB groups with anisole gave the unprotected β-keto amide as a separable 1:1 mixture of keto (shown in Scheme 1) and enol tautomers. "Only the keto tautomer could be cyclized with NaOMe by a Dieckmann condensation to afford pure aurantoside G in quantitative yield (3.7% overall yield). The enol tautomer needed to be re-equilibrated with acid to give the initial mixture of tautomers," said Professor Schobert, adding: "There are several lessons we have learned from this synthesis: the PMB groups were crucial for its success by enabling the Fukuyama–Mitsunobu reaction *electronically* (electron-releasing effect) and by controlling the β-selective *N*-acylation *sterically*. The Dieckmann cyclization may be used for the synthesis of even delicate tetramic acids. It does not give rise to partial racemization at the C-5 of the heterocycle, nor does it interfere with highly unsaturated fragments or unprotected sugars. So, this synthetic route should be applicable also to other, more complex *N*-β-glycosylated congeners of aurantoside G."

Professor Schobert concluded: "The mind-boggling sensitivity of aurantoside G – after all a natural product! – is not without precedence. Kalesse and Hartmann had a similar experience with the related lipomycins.[6] What might stabilize such compounds within the producing organism is an interesting question to muse on."

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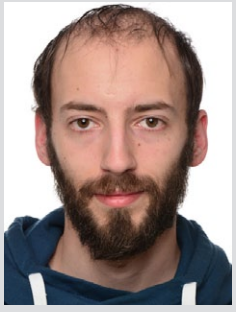
About the authors

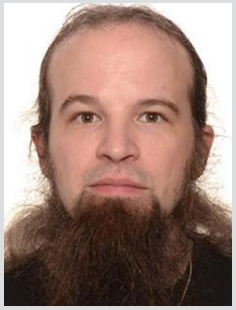
Prof. R. Schobert

Rainer Schobert received his doctoral degree in 1985 for synthetic work on macrolide antibiotics in the group of Hans-Jürgen Bestmann at the University of Erlangen (Germany). After a postdoctoral project on organoiron chemistry with Steven Ley at the Imperial College in London (UK) he went back to Erlangen to finish his habilitation on early transition metallocenes in 1993. Between 1999 and 2001 he was a senior lecturer at The Queen's University Belfast (UK). He currently holds the Chair of Organic Chemistry at the University of Bayreuth (Germany). His research interests span a wide range including bioactive lactones and lactams, siderophore-penam conjugates, and anticancer metallodrugs.



M. Petermichl

Markus Petermichl obtained his B.Sc. (2012) and his M.Sc. (2015) degrees in chemistry for his synthetic studies of the chemistry of complex acyltetramic acids in the group of Professor R. Schobert at the University of Bayreuth (Germany). He stayed in the group for a Ph.D. project and is currently pursuing total syntheses of further glycosylated tetramic acids and of other natural heterocycles with biological activity.



Dr. S. Loscher

Sebastian Loscher studied chemistry at the University of Stuttgart (Germany). After research internships with Professor K. Kern at the Max Planck Institute for Solid State Research (Germany) in 2005 and with Professor P. H. Seeberger at the ETH Zürich (Switzerland) in 2008, he undertook a diploma project in 2009 on α-glucosidase inhibitors with Dr. T. D. Butters at the Oxford Glycobiology Institute (UK). In 2010, he joined the group of Professor R. Schobert to work on the total synthesis of glycosylated tetramic acids until his graduation in summer 2015. Since September 2015 he has been a postdoctoral fellow in the group of Professor Dr. M. Bogyo in the Department of Pathology at Stanford University (USA).