Asymmetric One-Pot Transformation of Isoflavones to Pterocarpans and Its Application in Phytoalexin Synthesis

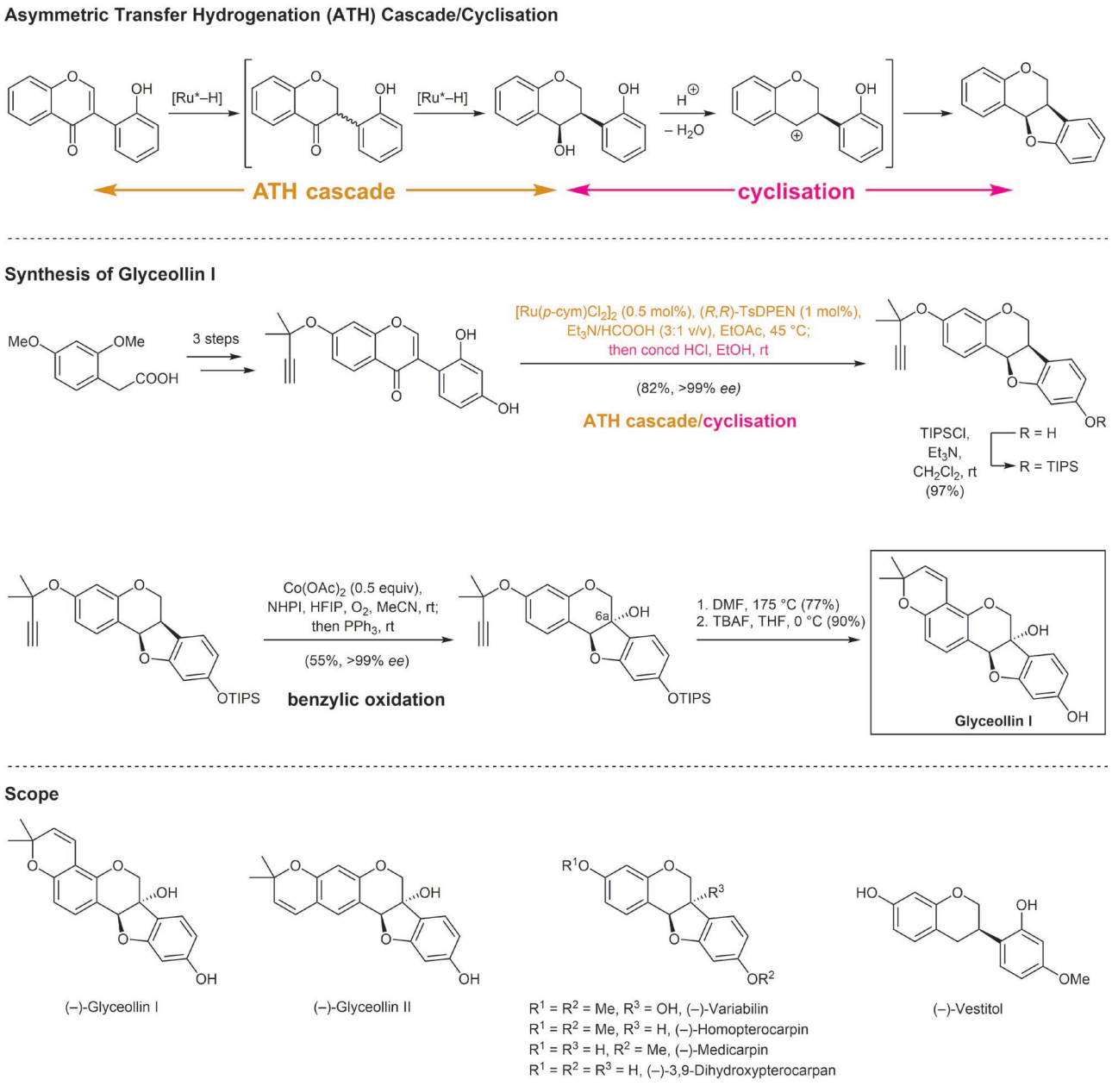
Nat. Commun. **2020**, DOI: 10.1038/s41467-020-16933-y

Phytoalexins are structurally diverse, low-molecular-weight secondary metabolites that are produced *ex novo* in appreciable amounts by plants following a pathogenic attack. These antimicrobials may be isolated from stressed soy plants and, owing to their interesting biological properties, have attracted the attention of many research groups in recent years. Some phytoalexins have shown capacity for selectively modulating the activity of the oestrogen receptor, which plays an important role in the growth of oestrogen-related cancers, e.g. mammary carcinoma or ovarian cancer. Furthermore, their anti-inflammatory and anti-cholesterolemic activity, as well as further health-promoting effects, are under investigation all over the world.

However, the isolation of the pure phytoalexins from natural sources is generally challenging. The development of a concise catalytic access to structurally defined phytoalexins, such as the enantiopure pterocarpans glyceollin I and glyceollin II, is an important entry to these compounds and was the driving force of the research described in a paper recently published by Professor Peter Metz and Dr. Philipp Ciesielski (Technische Universität Dresden, Germany). Professor Metz commented: "With our work we wanted to make these phytoalexins and further isoflavonoids more readily available, especially for detailed studies on their bioactivity."

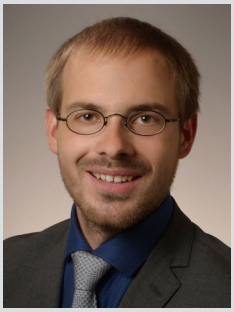
Professor Metz noted that a common pathway for the enantioselective construction of the 6a-hydroxypterocarpan skeleton of several phytoalexins is the Sharpless asymmetric dihydroxylation (SAD) of a suitable isoflav-3-ene. But as the SAD of isoflav-3-enes requires stoichiometric amounts of the toxic and expensive osmium tetroxide and of chiral ligand as well – as demonstrated in the first asymmetric synthesis of glyceollin I by the Erhardt group (University of Toledo, USA) – a novel catalytic access was desirable (for references, see the original paper).

"Some years ago, we found that a ruthenium-catalysed asymmetric transfer hydrogenation (ATH) of racemic isoflavanones succeeds with a highly selective dynamic kinetic resolution to give the corresponding enantiomerically pure isoflavan-4-ols in yields exceeding 90%," said Professor Metz. He continued: "Now, for the first time, we were also able to use an isoflavone as a substrate for ruthenium-catalysed ATH. In this process a conjugate reduction to a racemic isoflavanone is carried out first, which is then reduced with dynamic kinetic resolution. Aiming for the pterocarpan skeleton, the ATH can be quenched with hydrochloric acid after dilution with ethanol to achieve a smooth cyclisation." Searching for suitable conditions for the regioselective installation of the benzylic hydroxyl group at C-6a, the authors found an adapted protocol from the group of Ishii (Kansai University, Japan), which was superior to the other methods tested. "Indeed, we believe we are the first to apply this aerobic oxidation to a complex molecule," explained Professor Metz. He concluded: "Using this biomimetic strategy, only eight steps were necessary to secure glyceollin I in good overall yield from the commercially available (2,4-dimethoxyphenyl)acetic acid. Furthermore, our approach – illustrated in Scheme 1 – gave access to several other naturally occurring phytoalexins in an efficient manner and high enantiomeric purity."



Scheme 1 Asymmetric transfer hydrogenation cascade/cyclisation in the synthesis of glyceollin I and scope of the phytoalexins synthesised

About the authors



Dr. P. Ciesielski

Philipp Ciesielski studied chemistry at the Technische Universität Dresden (Germany) and obtained his MSc degree in 2014. During his PhD studies under the supervision of P. Metz he focused his research on the development of asymmetric total syntheses of bioactive isoflavonoids. He received his PhD in 2019.

Prof. P. Metz

Peter Metz studied chemistry at the University of Münster (Germany), where he received his Diploma (1979) and PhD (1983) under the guidance of H. J. Schäfer. After a postdoctoral research stay with B. M. Trost (1983–1984; University of Wisconsin-Madison, USA), he returned to Münster and completed his Habilitation in 1991. Following temporary full professorships at the University of Hamburg (Germany, 1992–1993), the University of Kiel (Germany, 1994) and the Technische Universität Dresden (Germany, 1996), he became a full professor at the TU Dresden (1997). His research interest covers the total synthesis of biologically active natural products and their analogues, as well as the development of novel methods and strategies for stereoselective synthesis.

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