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Strigolactones: Plant Hormones with Promising Features

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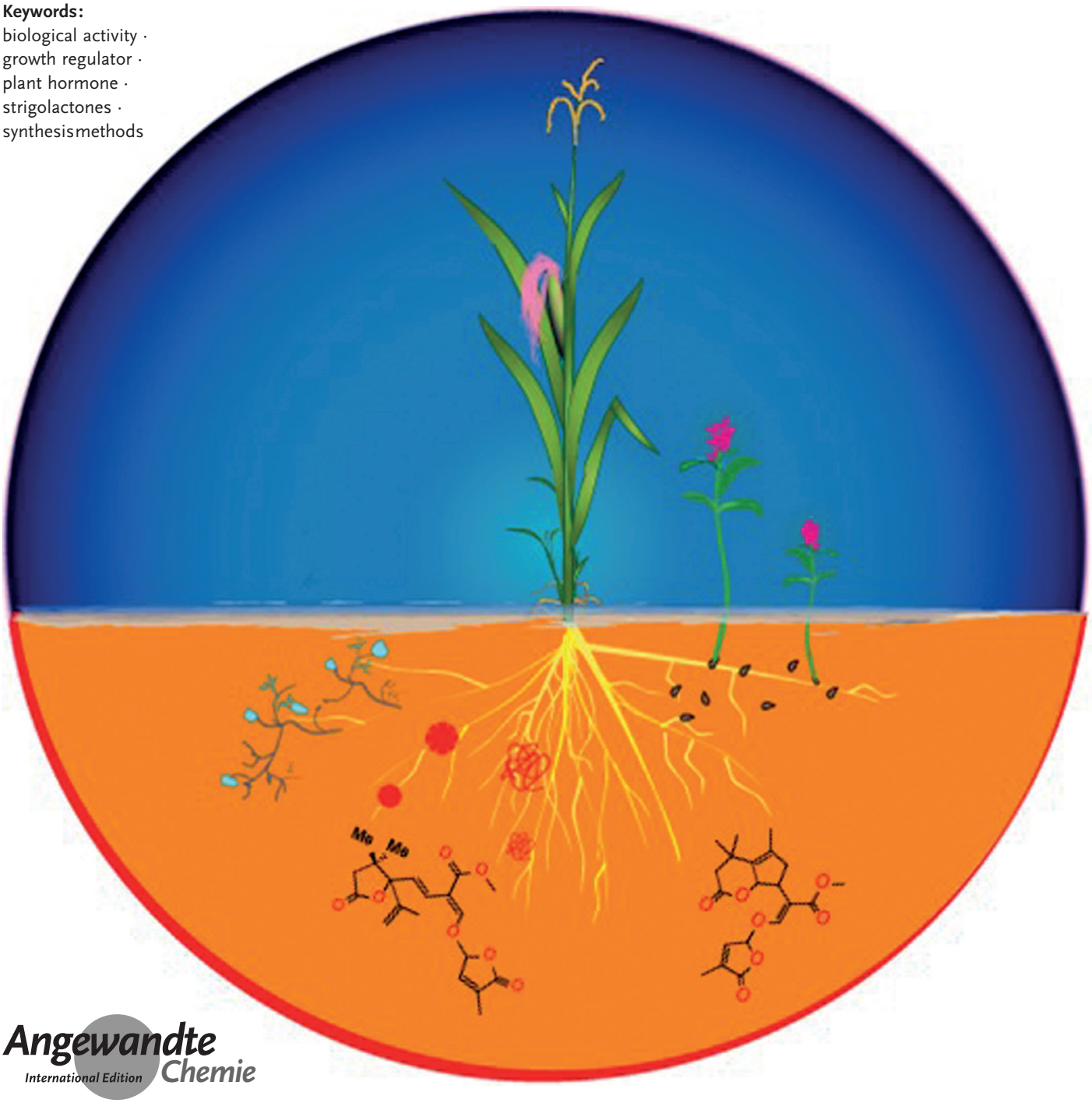

Almost 80 years after the discovery of the first plant hormone, auxin, a few years ago a new class of plant hormones, the strigolactones, was discovered. These molecules have unprecedented biological activity in a number of highly important biological processes in plants but also outside the plant in the rhizosphere, the layer of soil surrounding the roots of plants and teeming with life. The exploitation of this amazing biological activity is not without challenges: the synthesis of strigolactones is complicated and designing the desired activity a difficult task. This minireview describes the current state of knowledge about the strigolactones and how synthetic analogs can be developed that can potentially contribute to the development of a sustainable agriculture.

1. Introduction

Eighty years after the elucidation of the structure of the first plant hormone, auxin,[1] the latest discovery of a new class of plant hormones, the strigolactones, was reported.[2,3] In this work it was shown that the elusive inhibitor of plant branching[4] actually are the strigolactones (Figure 1).[2,3] Intriguingly, the discovery that strigolactones are a plant hormone occurred about 50 years after the identification of the first strigolactone, strigol.[5] Strigol was isolated from the root exudate of cotton as the germination stimulant of the parasitic weed, *Striga lutea*.[5] The latter is a root parasitic weed from the plant family *Orobanchaceae,* which includes broomrapes and witchweeds. These parasitic weeds represent a severe problem in agriculture, particularly in crops such as tomato, rapeseed, sunflower, legumes, maize, sorghum, and millet.[6] They grow on the roots of their host and totally depend on that host for survival and reproduction. They have partially or completely lost photosynthesis and rely on their host for assimilates, water and minerals. Also for their germination they rely on their host: they only germinate upon perception of the germination stimulant that is secreted from the roots of their host, the strigolactones (Figure 1).[7,8] To date, at least 25 different strigolactones (a name coined by Larry Butler[9]) have been identified, with different plant species usually exuding different blends of several different strigolactones.[10,11]

2. Biological Properties of Strigolactones

A number of years before the discovery of the plant hormone role of the strigolactones, light was shed on the enigma why plants secrete these strigolactones into the soil. In 2005 Akiyama et al. reported that strigolactones induce hyphal branching in arbuscular mycorrhizal (AM) fungi (Figure 1).[12] Most land plants engage in a symbiotic interaction with these AM fungi that supply water and nutrients to the plant, in return for photoassimilates from the plant.[13] This discovery led to the conclusion that plants secrete strigolactones to recruit AM fungi and that parasitic plants have hijacked this signaling molecule to ensure germination in the proximity of a host root.

After the discovery of their shoot branching inhibiting effect, further studies showed that strigolactones also regulate other aspects of plant development including root architecture, secondary stem growth, and leaf senescence.[14,15] The strigolactones seem to be particularly important for the regulation of plant development in response to changes in environmental conditions such as phosphate availability and drought.[16,17] Intriguingly, plants seem to kill two birds with one stone by using the strigolactones to adapt their development (adapting root and shoot architecture to conditions of insufficient phosphate[17,18]) and at the same time call in the help from others to deal with these adverse environmental conditions (stimulate colonization by AM fungi that will forage for phosphate that is out of reach or otherwise not available to the plant[12]).

It is becoming clear that the strigolactones have additional roles—as plant hormones—and, just as other plant hormones such as auxin, regulate many different processes.[14] It will be highly interesting to see if all these processes are related to the response of plants to abiotic stresses.[19,20] In addition, it is also not unlikely that their rhizosphere signaling role is broader than just the AM fungi, which would then perhaps also explain why plants secrete so many different strigolactones.[10] Indeed, there are indications that strigolactones also positively affect nodulation and hence nitrogen fixation by plants[21] and in a preliminary study with sorghum genotypes differing in their root exudate strigolactone composition, also differences in the bacterial root microbiome composition were detected.[22] Although a number of studies have attempted to demonstrate a role for strigolactones in the interaction of plants with pathogenic micro-organisms and insects, the evidence that this is the case is not very strong.[23]

3. (Bio)synthesis of Strigolactones

The discovery in 2008 that the strigolactones are the elusive branching inhibiting hormone[2,3] resulted in a relatively fast elucidation of the core strigolactone biosynthesis pathway. This pathway consists of a ß-carotene isomerase (DWARF27) and two carotenoid cleavage dioxygenases

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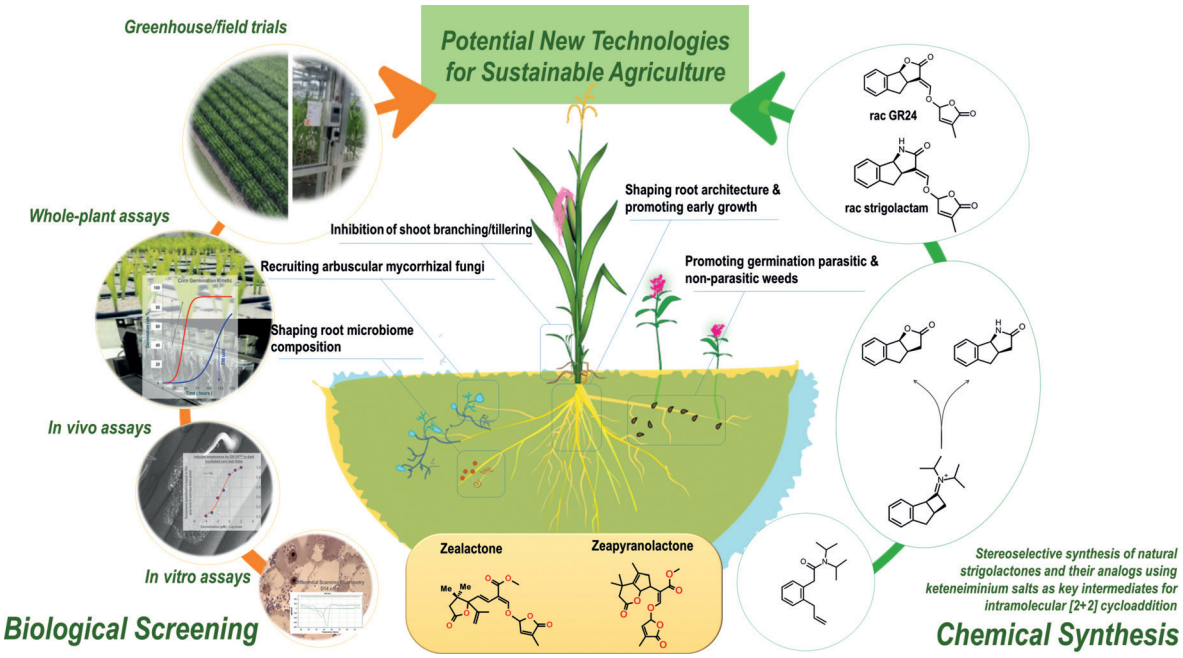

Figure 1. Plants produce strigolactones, such as the non-canonical maize strigolactones zealactone and zeapyranolactone (bottom). Strigolactones have an endogenous signaling role as plant hormone affecting, for example, root architecture and shoot branching/tillering (center). Strigolactones are also secreted into the soil where they induce hyphal branching in AM fungi and germination of parasitic plants (center). Chemical synthesis of natural strigolactones and of improved strigolactone analogs (right) allows for the evaluation of the biological relevance of strigolactones as well as their potential for applications in agriculture. This is assessed using in vitro, in vivo, and whole-plant assays and selected compounds are further examined through greenhouse and field trials (left).

Harro Bouwmeester received his Master's degree and PhD in Plant Physiology from Wageningen University, the Netherlands (1985, 1990). After postdoctoral and research scientist appointments in several research institutes in Wageningen, he became Chair of Plant Physiology at Wageningen University (2008). Since 2016 he is Chair of Plant Hormone Biology at the Swammerdam Institute for Life Sciences (SILS) of the University of Amsterdam, the Netherlands. The work in his group is centered around signalling molecules and their role in the chemical communication of plants with other organisms. Together with the other co-authors of the present minireview she was awarded the SCS Sandmeyer Award in 2018.

Claudio Screpanti obtained his PhD in Agronomy from the University of Bologna, Italy in 2004. He carried out additional studies in molecular biology and genetic engineering at the University of Louvain-la-Neuve, Belgium. In 2005 he joined the Syngenta R&D organization. In 2018 he became a Syngenta Fellow. In his current role, he leads the Soil Competence Centre and acts as Syngenta soil expert looking at the soil behavior of new small molecules. The aim is to discover and develop new and more sustainable crop protection solutions. Together with the other co-authors of the present minireview he was awarded the SCS Sandmeyer Award in 2018.

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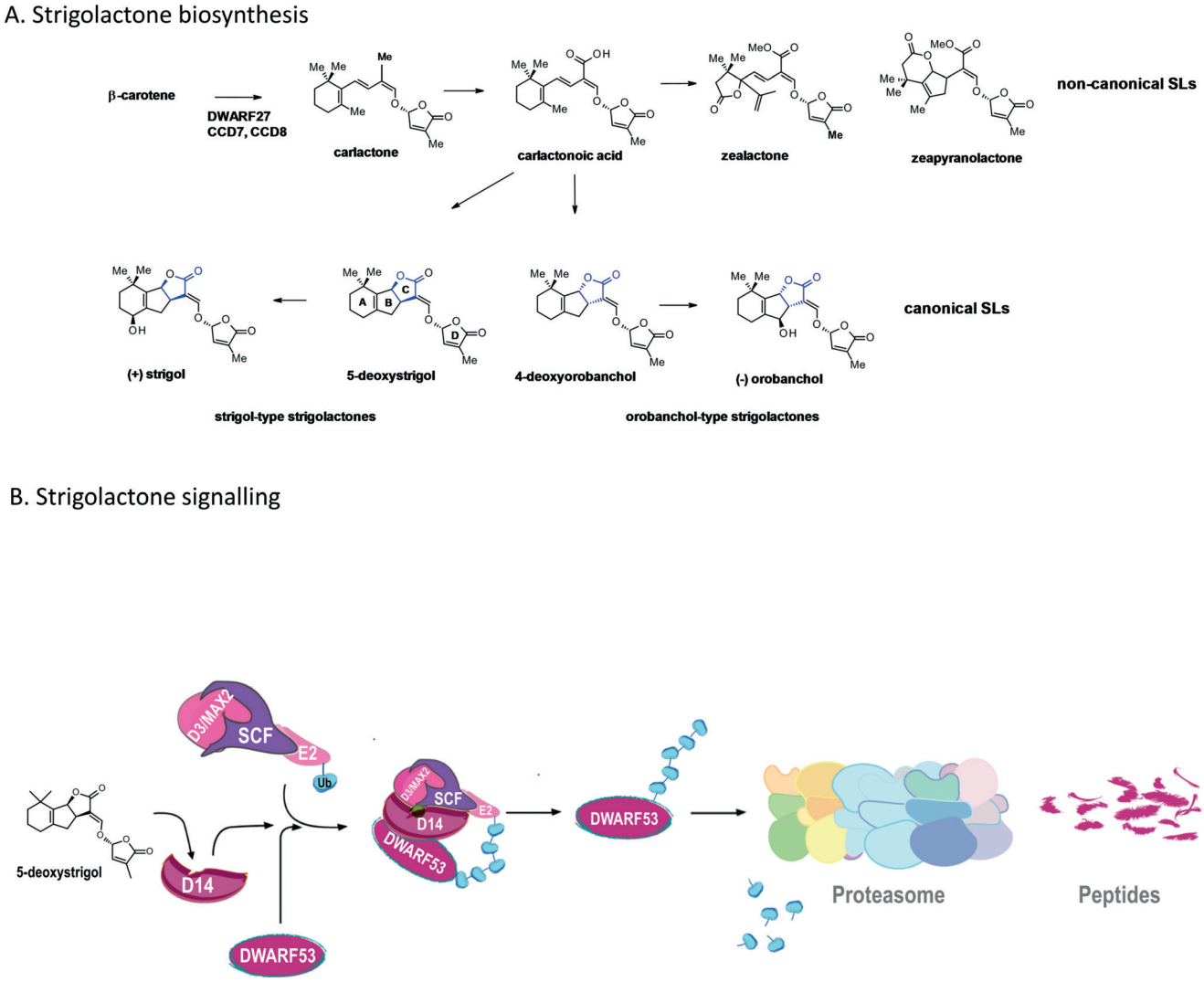
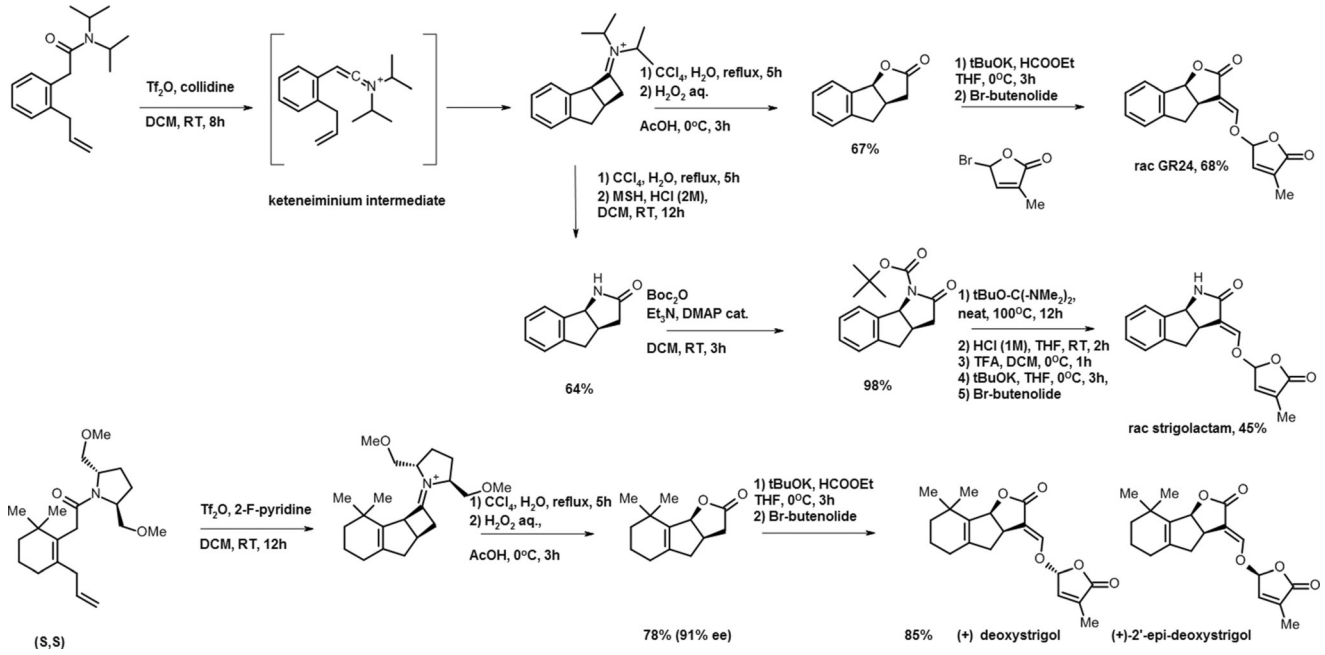


Figure 2. A) Strigolactone biosynthesis from β-carotene involves enzymes, DWARF27 (β-carotene isomerase) and CCD7 and CCD8 (carotenoid cleavage dioxygenases 7 and 8) that produce carlactone, which is further transformed, a.o. by MAX1 (a cytochrome P450) into canonical strigolactones (with the tricyclic ABC ring structure) and non-canonical strigolactones, such as zealactone and zeapyranolactone from maize. B) Upon binding of a strigolactone to the receptor D14, the conformation of D14 changes such that it can recruit the F-box protein MAX2/D3, which targets repressor proteins DWARF53 and SMXLs for ubiquitination and proteasomal degradation resulting in the induction of gene expression and therefore changes in plant development such as the inhibition of bud outgrowth. The strigolactone, 5-deoxystrigol, is used as an example. Ub indicates ubiquitin.

(CCD7 and CCD8) and produces carlactone, which we assume is the precursor for all known strigolactones (Figure 2).[24] After carlactone, strigolactone biosynthesis strongly diverges; on the one hand into strigol- and orobanchol-type strigolactones, on the other into non-canonical strigolactones that do not have the classic ABC-ring structure that the canonical strigolactones have (Figure 2).[10] Our knowledge about the details of strigolactone biosynthesis after carlactone is limited to the identification of a number of enzymatic steps in *Arabidopsis* (towards a non-canonical strigolactone) and rice (towards orobanchol-type strigolactones) (Figure 2).[10,25–27] This limited knowledge is illustrated by the recent identification of, non-canonical, maize strigolactones with quite exceptional structures of which biosynthesis is as yet totally unknown (Figure 2).[28,29]

Just as for the first plant hormone to be discovered, auxin, the development of synthetic analogs of strigolactones will be decisive to fully understand their biological relevance and explore applications in agriculture (Figure 1). Strigolactones are produced by plants in pg quantities[30] and therefore access to synthetic strigolactones as well as to modified/improved analogs is of prime importance. Several groups have done pioneering work on the synthesis of natural and synthetic analogs and particularly Zwanenburg's group.[31–35] We contributed with the development of a novel stereoselective synthesis of strigolactones that uses keteneiminiums as key intermediates for intramolecular [2+2] cycloaddition to a C=C bond, resulting in the corresponding cyclobutane iminium salt, which is readily hydrolyzed to cyclobutanone and further transformed into the corresponding lactone and lactam (Scheme 1).[36–40] Racemic GR24, which is widely used as



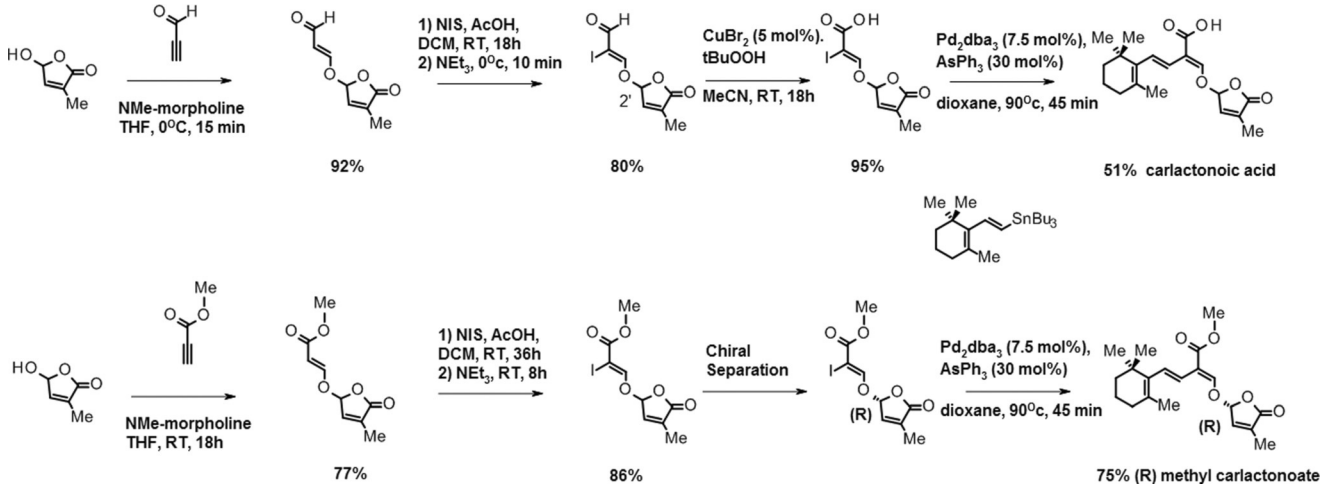
Scheme 1. Stereoselective synthesis of natural strigolactones and of their analogs using intramolecular [2+2] cycloaddition of a keteneiminium intermediate.

a standard for biological evaluation, could easily be produced by formylation of an achiral amide and coupling to the D-ring chloro-butenolide.[36–40] Similarly, a variety of strigolactam derivatives were synthesized that display similar and frequently superior biological activity compared to that of the corresponding lactones.[36–39] The use of a chiral auxiliary on the starting amide allows the highly stereoselective synthesis of various strigolactone/strigolactam analogs as well as natural strigolactones. For example, (+)-5-deoxystrigol was obtained in high overall yield with very good stereoselectivity (*ee* 92%) just like the other three stereoisomers of deoxystrigol/deoxyorobanchol, which is important for the evaluation of their biological activity.[41]

Non-canonical strigolactones, which do not display the canonical ABC tricyclic structure, are either key biosynthetic intermediates such as carlactone, carlactonoic acid, and methyl carlactonoate, or are also isolated as major strigolactone end-products from various plant species.[28,29,42] For access to these non-canonical strigolactones, a novel synthesis was developed for methyl carlactanoate and carlactonoic acid, which can be obtained either as a racemic mixture or in an optically pure form using the corresponding vinyliodides (Scheme 2).[42]

4. Biological Activity of Synthetic Strigolactones

Similar to other plant hormones such as auxin, the strigolactones require a receptor to have an effect on biological processes. Also here the branched phenotype of



Scheme 2. Synthesis of the non-canonical strigolactones, methyl carlactonoate and carlactonoic acid.

mutants has helped in the identification of components involved in strigolactone perception and downstream signaling. This includes the discovery of two canonical α/β hydrolase fold proteins, the strigolactone receptor, D14, and the homologous receptor, D14-like/KAI2/HTL (further abbreviated as HTL).[15] Intriguingly, although D14 is a receptor it retains its hydrolase activity and upon protein–ligand interaction, the strigolactone ligand is hydrolyzed (Figure 2).[43,44] Although crystallography suggests that the presence of the D-ring in the active site is required for the interaction of D14 with MAX2, the jury is still out on whether hydrolysis is necessary for signaling or a consequence.[43,45] Upon binding of a strigolactone/the D-ring, the conformation of D14 changes such that it can recruit the F-box protein MAX2/D3 (Figure 2). MAX2/D3 targets repressor proteins, DWARF53 and SMXLs, for ubiquitination and hence proteasomal degradation. This results in the induction of gene expression and therefore leads to changes in plant development such as the inhibition of bud outgrowth (Figure 1, Figure 2).[14,15] Where D14 has now been proven to be the receptor involved in the regulation of plant development by strigolactones, HTL was, in a series of beautiful papers, shown to have duplicated and evolved new ligand-binding specificity in the root parasitic broomrapes and witchweeds.[46,47] This allowed these parasites to germinate upon perception of strigolactones secreted by their host. Intriguingly, the exact role and ligand of HTL in other non-parasitic plants remain elusive up to date.[15]

The availability of the strigolactone receptor allows us to use this as a tool to screen for ligands (Figure 1). This is nicely illustrated by the work of Uraguchi et al. in 2018 who used the HTL of the parasitic weed, *Striga hermonthica,* to look for active synthetic germination stimulants.[48] For a number of different plant species such as rice, Arabidopsis and petunia, the crystal structure of D14 has been obtained.[48–50] These structures have very similar topologies but subtle differences in their binding pockets could perhaps influence the affinity to (synthetic) strigolactone (analogs). Structural information about the ligand-binding site is a key tool for the design of new synthetic analogues through docking studies and analysis of the interaction between the ligand and active site residues. This powerful technique was used to create synthetic debranone derivatives with highly improved *S. hermonthica* seed-germination-inducing activity.[43,45,51] As for other plant hormones, affinity measurements can be done using several techniques such as isothermal titration calorimetry (ITC)[52] or monitoring thermal destabilization of the receptor as induced by strigolactones.[53] The use of fluorogenic molecules like yoshimulactone green (YLG)[54] that fluoresce upon hydrolysis, can proivde information about the chemical scaffolds of the synthetic molecules that efficiently compete with its binding as described for *S. hermonthica* HTL7.[48,55] An in vitro yeast-two-hybrid assay has been developed to provide information on the strigolactone-promoted D14 interaction with MAX2/D3.[53] StrigoQuant is a biological sensor that monitors strigolactone activity by measuring D14-induced degradation of AtSMXL6 coupled to a luciferase in Arabidopsis protoplasts.[56] Along a similar line, Arabidopsis expressing D14 fused to a luciferase can provide information about D14 degradation upon the application of (synthetic) strigolactones and hence provide quantitative activity information.[57] Finally, structure–activity relationship (SAR) studies can be done in planta—by monitoring strigolactone-induced phenotypes such as leaf senescence and inhibition of branching—to analyse strigolactone analog potency (Figure 1).[51,58–60]

5. Possible Uses for a Sustainable Agriculture

Plant hormone-based technologies to control crop development and mitigate stress are well adopted in agriculture.[61] The role that the strigolactones play in the adaption of plants to abiotic stress makes them an interesting target for applications in sustainable agriculture.[8,19,20] Considering the so far discovered effects of strigolactones, the most important application domains encompass drought mitigation, nutrient assimilation efficiency, and promotion of early crop development. Drought mitigation is highly relevant with the increasing episodes of erratic rainfall during cropping seasons due to climate change.[62] Increasing nutrient assimilation efficiency and improving early crop development are other very relevant traits for the promotion of conservation agriculture, a core part of sustainable agriculture strategies.

Although several studies demonstrated the involvement of strigolactones in the plant response to drought,[63–66] additional efforts are needed to fully understand the underlying mechanisms. Other studies showed that foliar application of GR24, a synthetic strigolactone analog, on *Arabidopsis thaliana* or grape can mitigate the effects of drought.[63,67] These studies provide preliminary evidence that exogenous application of synthetic strigolactones seems to mitigate adverse effects of drought stress. Crop enhancement products based on plant hormones have been developed[61] and thus it is conceivable that synthetic analogs of the strigolactones can be optimized and can be used in the field. However, for applications in agriculture, much more knowledge is required about, for example, the bioavailability and stability in planta and in soil and the degree of uptake following application under field conditions. Due to the very high intrinsic activity of strigolactones in vitro, the optimization of the above-mentioned bioavailability aspects can potentially result in very low field application rates in the range of 1–10 grams/hectare. This can have positive implications for costs, and environmental and human safety.[19]

As a result of the increase in conservation agriculture, including the use of no or minimum tillage practices,[68] crops face environmental challenges, especially during early establishment, such as low soil temperature and soil compaction,[69] which can delay early crop establishment and thus negatively affect yield. Under controlled conditions, strigolactones can alleviate thermoinhibition of germination in several different species,[8,39,70] but application under field conditions will need further investigation. Fast degradation of natural and synthetic strigolactones in soil[39] and limited information about the early chemical uptake into the seed[40] can be the major factors influencing the activity in the open field.

Several studies have demonstrated that natural or synthetic strigolactones (e.g. GR24) promote plant growth and influence the architecture of roots in several different species (Figure 1).[18,71] Good root vigor during early crop establishment particularly under adverse soil conditions (i.e. low temperature or soil compaction) is a highly desirable trait. This also holds for the adaptation of root architecture to patchy nutrient availability in the soil, particularly phosphorus, in which strigolactones may also play a role. These positive effects make strigolactones an interesting target for the development of crop-enhancement products.

In addition to the role of strigolactones in the recruitment of AM fungi and nitrogen fixing *Rhizobacteria* as mentioned above, an effect on other microbial species cannot be excluded (Figure 1). The potential role of strigolactones in shaping the root microbiome has been suggested by several groups[22,72,73] and the recent advances in sequencing technologies and analysis will most likely soon result in new findings in this area.[72] This may open up new opportunities for innovation through breeding of new crop varieties with a balanced exudation of strigolactones to selectively recruit specific beneficial microorganisms.

Despite the fact that several "proofs of principle" on the potential application of strigolactones in agriculture exist, future and continued R&D investments will be critical to the successful development and use of this type of technology in agriculture.[19] In addition, clarity is needed on the legislation around production, commercialization and use of potential future strigolactone-based technologies in agriculture.[74] This legislation will strongly affect the required investments in money and time to bring any strigolactone-based technology to the market and hence to the farmers.

6. Summary and Outlook

The first strigolactone, strigol, was identified over 50 years ago and for many decades we did not know much more about the strigolactones than that plants produce several different variants and that these induce germination of seeds of root parasitic plants. With the discovery that the strigolactones are also a plant hormone and have other signaling functions in the rhizosphere suddenly our knowledge has greatly expanded. We know now that the strigolactones play a crucial role in the adaptation of plants to especially abiotic stress, both through changes in plant development and through changes in the recruitment of helper micro-organisms, such as AM fungi. Together, this makes the strigolactones an attractive target for the development of synthetic plant enhancement chemicals for a modern and more sustainable agriculture. Our greatly improved understanding of strigolactone (bio)synthesis, perception and downstream signaling are key in an efficient development of these possibilities. More fundamental research on the roles of the strigolactones in and outside the plant will further fuel the development of strigolactones into the tools we will need to make modern-day agriculture more sustainable.

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Conflict of interest

The authors declare no conflict of interest.

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