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Total Synthesis and Stereochemical Confirmation of Heliolactone

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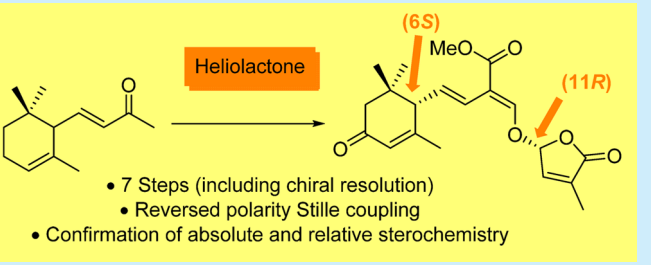
Supporting Information

ABSTRACT: Until now, the relative stereochemistry of the noncanonical strigolactone, heliolactone, has remained ambiguous. The total synthesis of heliolactone is described, with the key bond-forming event being a Stille cross-coupling that relied upon a reversal of the nucleophile−electrophile coupling partners. Spectroscopic analysis of synthetic heliolactone (and other stereoisomers) and comparisons with the isolated material enabled the absolute and relative stereochemistry of heliolactone to be secured.



The knowledge that small organic molecules affect plant growth is less than a century old,[1] and in 2008 a family of plant-derived compounds called strigolactones were identified as phytohormones that affect important aspects of plant growth and development (Figure 1).[2] In addition to the so-called "strigol-type" (**1**) and "orobanchol-type"(**2**) strigolactones which possess a common tricyclic core,[3] a subset of biosynthetically diverged strigolactones (**3**−**7**) have been isolated which are collectively known as "noncanonical" strigolactones (Figure 1).[4] Our interest was particularly drawn to heliolactone (**7**), which possesses the butenolide ring common to all strigolactones, but which also possesses a cyclohexenone fragment that is strikingly similar to the unrelated plant hormone, abscisic acid (**8**).[5] The possibility that heliolactone (**7**) functions as a multivalent ligand for both abscisic acid and strigolactone signaling receptors *in planta* offers exciting new directions for plant chemical biology and necessitates access to the naturally occurring compound.

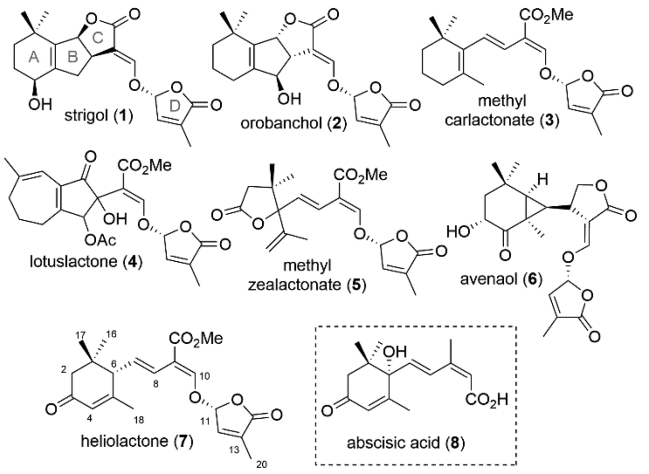


Figure 1. Selected strigolactones and abscisic acid.

Heliolactone (**7**) (Figure 1) was isolated from the root exudates of *Helianthus annuus* (the common sunflower) by Sugimoto and co-workers in 2014.[4e] The molecule presents a densely packed combination of synthetically challenging structural features, including a doubly vinylogous stereogenic center at C-6, and a configurationally defined cross-conjugated diene system. This renders both C-6 epimerization and isomerization of the C-7/C-8 alkene likely to occur via acid- and base-mediated mechanisms. The synthetic challenge is further magnified by the known sensitivity of the butenolide ring and the stereodefined C-11 acetal to moisture, acids, and bases.[6] The absolute stereochemistry of the C-11 stereocenter was based on the conserved stereochemistry across all strigolactones, and this was confirmed in biosynthetic studies in 2018.[7] In contrast, the absolute stereochemistry at C-6 was tentatively assigned by deconvolution of absorbance peaks in the CD spectrum of the isolated material. Due to significant spectroscopic overlap, that assignment remains ambiguous. The combination of biological function, stereochemical ambiguity, and chemical sensitivity make heliolactone (**7**) an important and challenging target for total synthesis.

Our initial synthetic strategy to heliolactone (**7**) was inspired by the recent work of De Mesmaeker and co-workers who reported the first synthesis of a noncanonical strigolactone, methyl carlactonate (**3**),[6] which employed a mild Stille cross-coupling as the key bond-forming reaction (Scheme 1).[8] We anticipated that stannane **11** and known iodide **10**[6] would undergo a similar cross-coupling and provide access to heliolactone (**7**).

As depicted in Scheme 2, our work began with the conversion of α-cyclocitral (**12**) into the corresponding dibromo-olefin **13**.[9] The electron-deficient nature of the olefin enabled subsequent allylic oxidation to occur on the cyclohexene ring to give enone **14**.[10] The enone unit was masked[11] as the enolate **15** before treatment with excess butyl lithium

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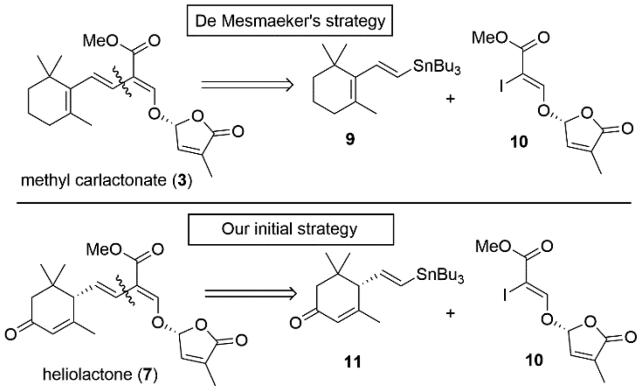
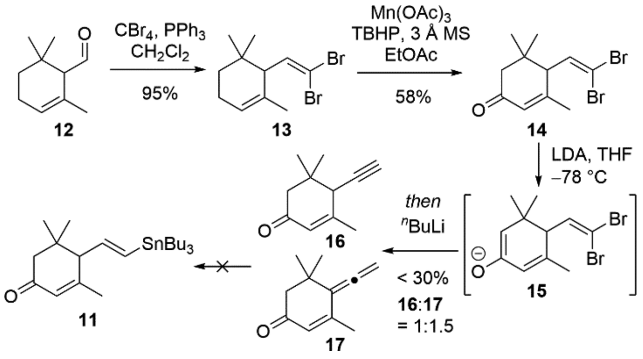
Scheme 1. Initial Retrosynthetic Analysis of Heliolactone (7)



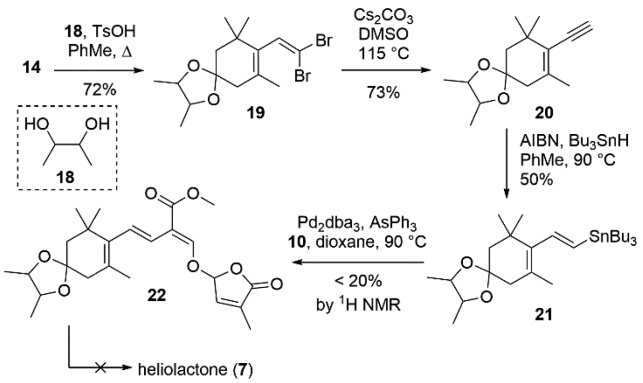
Scheme 2. Attempted Synthesis of Stannane 11



delivered the unstable alkyne **16** as the minor product in an inseparable mixture containing allene **17**. This proved inconsequential, as the mixture of **16** and **17** resisted hydrostannylation under a range of radical and palladium-catalyzed reaction conditions.[6,12]

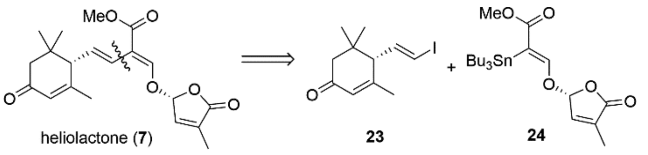
To temper the deleterious reactivity of the enone system and doubly allylic methine proton, compound **14** was converted into the corresponding acetal **19** (Scheme 3). The 4,5-dimethyl-1,3-dioxolane acetal was chosen following reports from Frackenpohl and co-workers that less substituted acetals (such as 1,3-dioxolane) were unstable on similar systems.[13] Acetal formation was accompanied by isomerization of the C-4/C-5 alkene into conjugation. The action of cesium carbonate in wet dimethyl sulfoxide effected conversion of the dibromo-olefin **19** into the alkyne **20**.[14] Hydrostannylation of **20** gave the *E*-configured stannane **21** in moderate yield and set the stage for the projected Stille cross-coupling. Frustratingly, subjecting **21** to De Mesmaeker's cross-coupling conditions with the known racemic iodide **10**[6] gave low yields (<20%) of the desired product **22** contaminated with a substantial proportion (40−50% by ^{1}H NMR analysis) of inseparable impurities resulting from decomposition of the D-ring (determined by characteristic aldehydic resonances in the chromatographically homogeneous material). Attempted mild *in situ* deprotection of the acetal and alkene isomerization of the product mixture containing **22** led to decomposition, and heliolactone (**7**) was not detected in the reaction mixture.

Scheme 3. Attempted Synthesis of Heliolactone (7) Using an Acetal Protected Strategy



Given the difficulties in generating the desired stannane **11** and the inability to successfully perform the Stille reaction−deprotection sequence with the protected variant **21**, we revised our synthetic strategy to invert the polarity of the coupling partners for the projected Stille reaction, which necessitated iodide **23** and alkenyl-stannane **24** (Scheme 4).

Scheme 4. Revised Retrosynthetic Analysis of Heliolactone (7)



The total synthesis of racemic heliolactone (±)-**7** (as a mixture of diastereomers) is shown in Scheme 5. While α-cyclocitral (**12**) resisted all attempts at Takai olefination,[15] the previously generated dibromo-olefin **13** was converted into the volatile alkyne **25**, which was immediately subjected to hydrostannylation and titration with iodine to give vinyl iodide **27** in good yield and high diastereoselectivity (*E*/*Z* 12:1) over the three-step sequence.[16] Our fears that the vinyl iodide would not be suitably electron-deficient to facilitate regioselective allylic oxidation proved unfounded and **27** was converted into the desired coupling partner **23**, with only a minor loss of diastereomeric integrity (*E*/*Z* 8.4:1). Similarly, conversion of the known vinyl iodide **10**[6] into the desired stannane **24** proceeded uneventfully.

With both coupling partners **23** and **24** in hand, the Stille cross-coupling reaction was optimized, and under room temperature conditions, racemic heliolactone (±)-(**7**) was isolated in good yield. It is noteworthy that only the desired *E*-configured olefin **27** participated in the palladium-catalyzed coupling, while the *Z*-isomer was not consumed.

Comparison of the NMR spectra of synthesized heliolactone (±)-(**7**) (a 1:1 mixture of C-6/C-11 *syn* and *anti* diastereomers) against authentic spectra of the isolated material confirmed the atom connectivity of the natural compound. Enantioselective HPLC separation of the mixture was only partially successful, with resolution occurring at the C-6 stereocenter to give two fractions, **7a** and **7b**. The chromatographically slower moving fraction exhibited a circular dichroism (CD) spectrum that closely aligned with the reported values for the isolated natural product. However, attempts to chromatographically separate the C-11 diastereomers or unambiguously assign the C-6 absolute stereochemistry proved unsuccessful. Therefore, the enantioselective total synthesis of heliolactone was undertaken.

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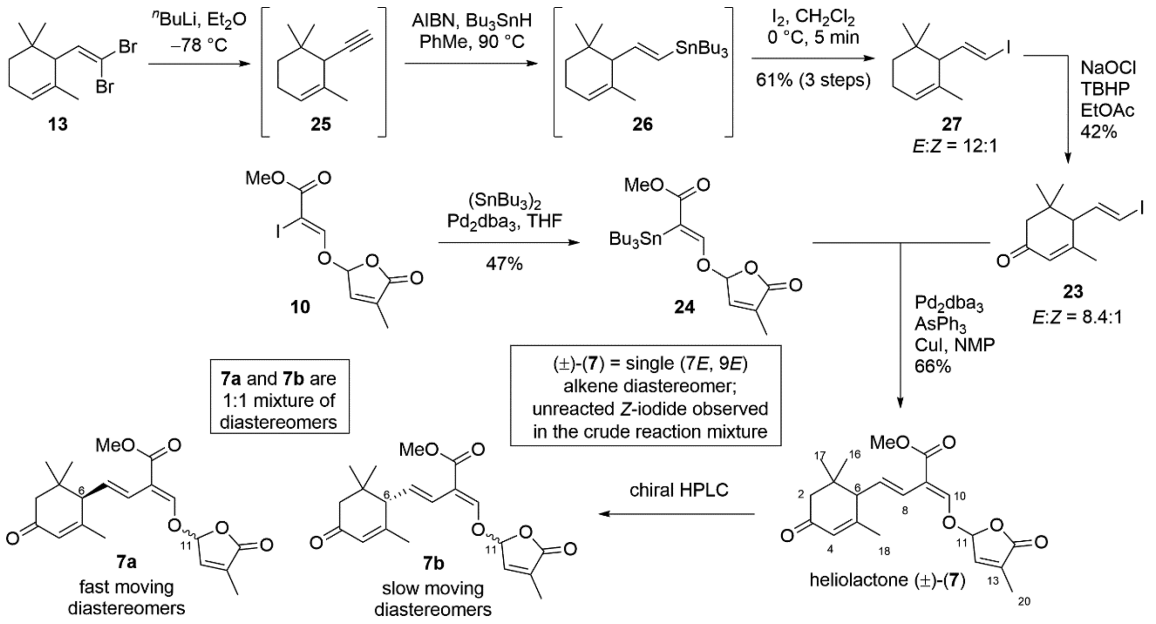
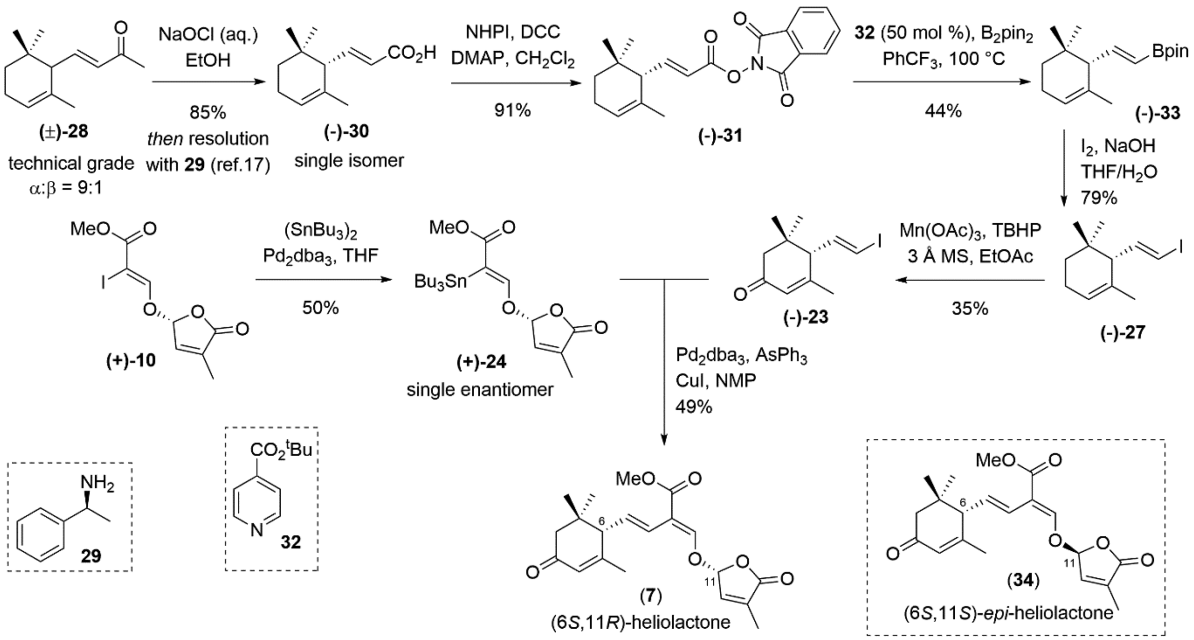
Scheme 5. Total Synthesis of (±)-Heliolactone (±)-(7)



Scheme 6. Enantioselective Synthesis of Heliolactone (7)[a]



[a]NHPI = *N*-hydroxyphthalimide, DCC = dicyclohexylcarbodiimide, DMAP = 4-*N*,*N*-dimethylaminopyridine, B_2pin_2 = bis(pinacolato)diboron, TBHP = *tert*-butylhydroperoxide, MS = molecular sieves, Pd_2dba_3 = tris(dibenzylideneacetone)dipalladium(0), NMP = *N*-methylpyrrolidinone.

As shown in Scheme 6, technical grade α-ionone (**28**) was subjected to a haloform reaction to give acid **30**. Resolution of the acid was achieved by formation of the diastereomeric salts using (*S*)-phenylethylamine (**29**) to give the *S*-configured acid (−)-**30**, according to the literature procedure.[17] Disappointingly, compound (−)-**30** resisted direct Hunsdiecker reaction,[18] necessitating a three-step sequence involving conversion into the activated ester (−)-**31**, amine-catalyzed borylation into (−)-**33**,[19] and iodination to deliver the required vinyl iodide (−)-**27**. Allylic oxidation delivered the single enantiomer coupling partner (−)-**23**. The second coupling partner (+)-**24** was synthesized from the known chiral iodide (+)-**10**[6] using palladium-catalyzed stannylation,[20] which proceeded with retention of absolute stereochemistry. Stille cross-coupling of (−)-**23** and (+)-**24** delivered heliolactone (**7**). Comparison of the NMR spectra and CD curves against the data for the isolated compound unambiguously showed that naturally occurring helioactone is the (6*S*,11*R*) isomer.

In a similar manner, enantiomeric stannane (−)-**24** was coupled with iodide (−)-**23** to give 11-*epi*-heliolactone (**34**). CD comparisons demonstrated that the slow moving mixture of diastereomers (**7b**) in Scheme 5 contained the (6*S*,11*R*) and (6*S*,11*S*) isomers.

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In summary, we report the first total synthesis of heliolactone (7). The racemic synthesis required 6 steps in the longest linear sequence (LLS), with 3 of those steps telescoped into a single operation. The enantioselective synthesis required 7 steps LLS, which included a chiral resolution. Comparison of the spectroscopic data for naturally occurring and synthetic heliolactone (7) secures the (6S,11R) stereochemistry for the natural product. The chemical biology of this noncanonical strigolactone can now be explored.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01402.

Experimental details, ^{1}H and ^{13}C NMR spectra, CD spectra, and HPLC traces (PDF)

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Notes

The authors declare no competing financial interest.

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