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Synthetic Access to Non-Canonical Strigolactones – Syntheses of Carlactonic Acid and Methyl Carlactonoate

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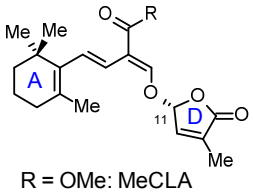
ABSTRACT. Strigolactones are plant hormones regulating essential stages of a plants development. Their low natural abundance combined with a low chemical stability significantly hampered the detailed investigation of their biological activity. Non-canonical strigolactones lack the fused tricyclic ABC-ring system commonly present in canonical-type strigolactones, but feature an open chain unit linking structurally diverse A-ring moieties to the butenolide D-ring.

We herein present an efficient synthetic access to enantiomerically pure non-canonical strigolactones by a Stille cross-coupling approach to forge the central diene moiety and demonstrate this strategy by

syntheses of natural products methyl carlactonoate (MeCLA) and carlactonic acid (CLA). Furthermore, a synthetic access to deuterium-labeled analogues of these natural products has been developed.



R = OMe: MeCLA
R = OH: CLA

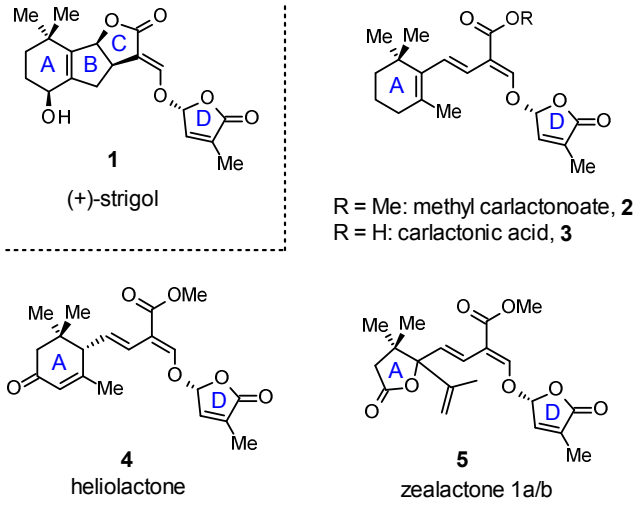
- **3/ 4 steps syntheses**
- **mild & versatile approach**
- **control of C11-stereocenter**
- **deuterium labeling**

INTRODUCTION. Strigolactones are terpenoid derived natural products that have recently been recognized as phytohormones involved in various stages of plant development.[1] After the first characterization of a strigolactone, isolated from root-exudates of cotton and named (+)-strigol (**1**, **Scheme 1**) in 1966,[2] more than 20 other strigolactones have been described in the following years.[3] Land plants, including higher plants but also non-vascular plants such as mosses, liverworts and stoneworts have been found to produce a plant specific variety of strigolactones. The so-called "canonical" strigolactones structurally consist of three fused rings (A, B, C) connected to a butenolide ring (D) via an enol ether bridge. These canonical strigolactones are biologically investigated in detail since the past decade and are involved in processes such as regulation of seed germination, seedling establishment, plant architecture as well as in soil signaling with arbuscular mycorrhizal fungi (AM fungi) and parasitic hosts. Several total syntheses and syntheses of analogues have been described which have contributed to the further understanding of the complex biology of strigolactones.[4,5]

Recently, a novel subclass of strigolactones has been identified, that lack the canonical ABC-ring moiety, but feature an open chain unit linking structurally diverse A-ring moieties to the D-ring. The structural and presumed biosynthetic "non-canonical" parent strigolactones are methyl carlactonoate **2** and carlactonic acid **3**, containing a β-ionone moiety as an A-ring (**Scheme 1**).[6,7,10] First biological studies show that they are potent inducers for germination[6] and for hyphal branching in AM fungi.[7] Further examples of non-canonical strigolactones are heliolactone (**4**)[8] bearing an oxidized A-ring and

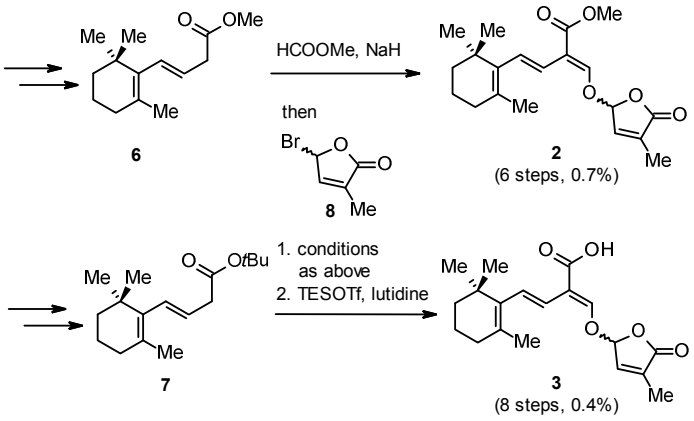
zealactone 1a/b (**5**)[9] containing an A-ring resulting from a formal oxidative rearrangement. Notably, zealactone 1a/b (**5**) has been reported as the most abundant strigolactone in corn, with heliolactone (**4**) being the most abundant in sunflower. These findings emphasize the potential high relevance of non-canonical strigolactones in crops.[9]

Scheme 1. Selected canonical and non-canonical strigolactones.



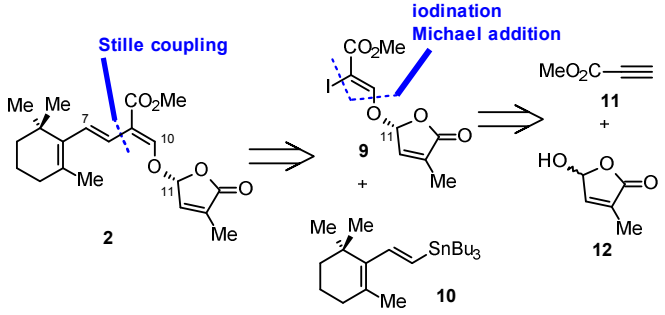
The low natural abundance paired with the intrinsic instability of non-canonical strigolactones towards acids and bases has so far hampered the investigation of these natural products. A single synthetic strategy for methyl carlactonoate (**2**) and carlactonic acid (**3**) has been reported by Akiyama, Yoneyama, Nomura and coworkers in 2014 (**Scheme 2**).[10] Their strategy consisted of a formylation of methyl- (**6**) or *tert*-butyl homodienyl ester **7** and alkylation of intermediary formed enolate using a bromo butenolide D-ring precursor **8**, in analogy to described syntheses of canonical strigolactones.[4] They were able to obtain racemic methyl carlactonoate (MeCLA, **2**) and racemic carlactonic acid (CLA, **3**) in six to eight steps and a low overall yield.

Scheme 2: Reported synthesis of MeCLA (**2**) and CLA (**3**).



We sought for a more general approach towards non-canonical strigolactones and identified the C7-C10 diene moiety to be possibly accessible by a Stille coupling of the known vinyl stannane **10**[11] with the novel vinyl iodide **9** (**Scheme 3**). Vinyl iodide **9** would arise from a Michael addition of butenolide alcohol **12** and methyl propynoate (**11**) and subsequent iodination. This strategy is shown in **Scheme 3** for MeCLA (**2**) but could be generally applicable to non-canonical-type strigolactones employing vinyl iodide **9** and suitable cross coupling partners. Furthermore, in contrast to reported syntheses of strigolactones,[4] control of the biologically relevant C11-stereocenter could be feasible by this approach.

Scheme 3: Retrosynthetic approach toward MeCLA (**2**).

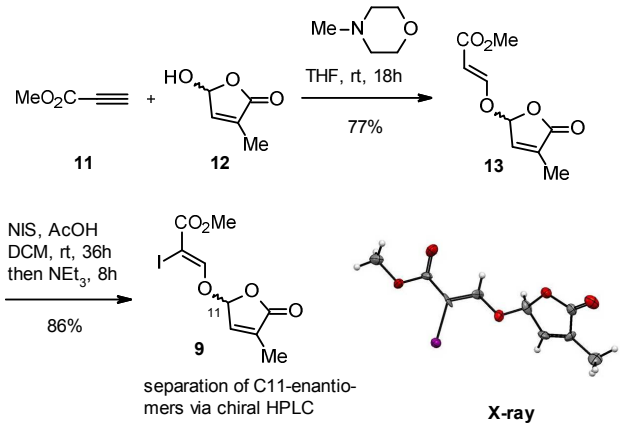


RESULTS AND DISSCUSSION.

Synthesis of vinyl iodide **9** started with Michael addition of commercially available butenolide alcohol **12** and methyl propynoate (**11**) in presence of *N*-methyl morpholine (see **Scheme 4**).[12] Notably, the *E*-configured alkene **13** was obtained as the only stereoisomer in 77% yield. Iodination of olefin **13** was achieved by treatment of **13** with a mixture of *N*-iodosuccinimide (NIS) and acetic acid followed by

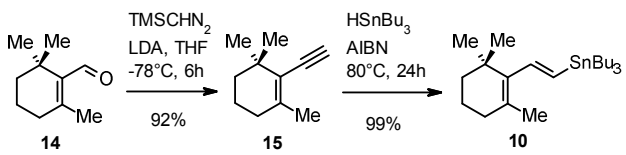
triethylamine. This regioselective iodoacetoxylation and in-situ base mediated acetate-elimination[13] furnished the desired vinyl iodide **9** in high yield of 86% and as a pure *Z*-configured diastereomer as confirmed by NMR-studies and X-ray structure analysis. Racemic **9** was obtained as bench-stable crystalline solid that could be readily separated into its C11-enantiomers (*R*)-**9** and (*S*)-**9** on gram-scale by HPLC on chiral stationary phase. The absolute configuration of the C11-stereocenter of both enantiomers (*R*)-**9** and (*S*)-**9** was elucidated via CD-analysis. Independently, a germination assay on *Orobanche Cumana*, known to highly favor strigolactone-type compounds containing the naturally occuring (*R*)-configured butenolide D-ring confirmed the absolute configuration.[5e]

Scheme 4: Synthesis of vinyl iodide **9**.



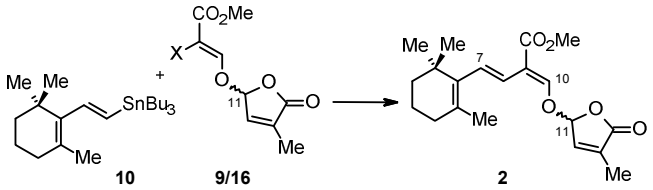
Synthesis of the vinyl stannane **10** proceeded by known alkynylation of β-cyclocitral (**14**)[14] using Colvin's procedure and hydrostannylation under modified radical conditions described by de Lera and coworkers (**Scheme 5**).[11] Vinyl stannane **10** decomposed upon attempted purification on silica gel, but was obtained in high purity by adding equimolar amounts of tributyl stannane to alkyne **15** under neat conditions with subsequent filtration over Celite.

Scheme 5: Synthesis of vinyl stannane **10**.



With both building blocks **9** and **10** in hand, we investigated suitable cross coupling conditions to build up the central C7-C10 diene-moiety as a common motif present in non-canonical strigolactones. Due to the pronounced lability of strigolactones under basic conditions, we focused on neutral Stille coupling conditions. Different catalytic systems were evaluated (entries 1-3, **Table 1**) showing that Pd_2dba_3/ $AsPh_3$ gave the most promising conversion and 30% isolated yield of the desired coupling product **2**. By employing an excess of stannane **10** (2.5 eq), the previously observed protiodehalogenation of vinyl iodide **9** could be suppressed. Further experimentation regarding catalyst loading, concentration, reaction time and temperature finally led to the optimized conditions to give racemic **2** in 75% yield (entry 4). Notably, the bromo-analogue **16** proved to be almost unreactive and gave only traces (<0.1%) of **2** (entry 5), presumably due to its lower reactivity towards oxidative addition with Pd(0). Enantiomerically pure vinyl iodides (*R*)-**9** and (*S*)-**9** gave natural product (+)-(*R*)-MeCLA and its enantiomer (−)-(*S*)-MeCLA without any observed C11-racemization.

Table 1.

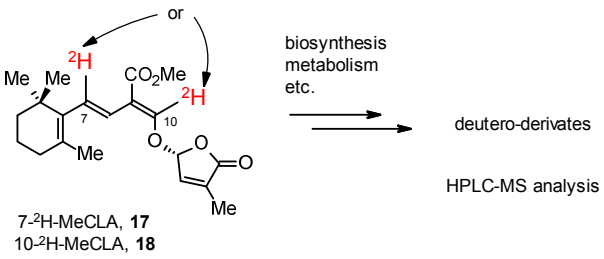


entry	'PdL$_n$'	X	conditions	Conversion / yield of **2**
1	$Pd(PPh_3)_4$ (20 mol%)	I	toluene, 100°C 60min	5% / traces
2	$PdCl_2(PPh_3)_2$ (20 mol%)	I	CuI, DMF 100°C 60min	full conv./ 10%
3	$Pd_2(dba)_3$ (10 mol%), $AsPh_3$ (40 mol%)	I	dioxane, 100°C 60min	full conv./ 30%
4	**$Pd_2(dba)_3$ (7.5 mol%), $AsPh_3$ (30 mol%)**	**I**	**dioxane, 90°C 45min**	**full conv./ 75%**
5	$Pd_2(dba)_3$ (10 mol%), $AsPh_3$ (40 mol%)	Br	dioxane, 100°C 60min	30% / traces

This developed route led to racemic methyl carlactonate (MeCLA, **2**) in three steps and an overall yield of 50% (longest linear sequence). Stability studies of MeCLA (**2**) either stored as neat product or in solution at different temperatures revealed a halflife-time of $t_{1/2} \sim 30$ d when stored as neat product or as solution in dichloromethane at -80 °C in the dark under argon.

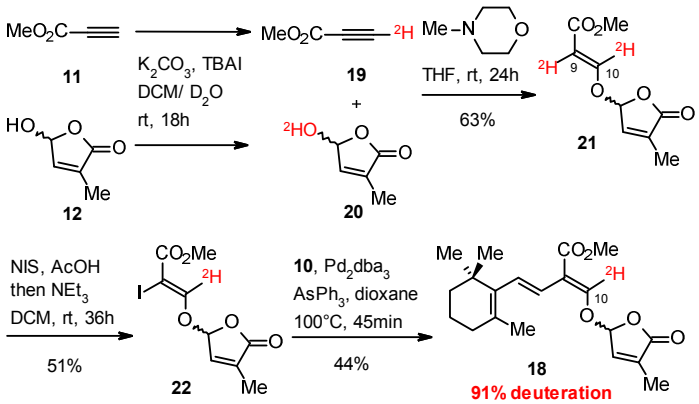
Isotope-labeled non-canonical strigolactones are valuable tools to study various biochemical processes such as biosynthetic pathways, metabolic behavior or transport processes. We thus sought for possible isotopes at optimal positions for MeCLA (**2**) and identified deuterated analogues **17** & **18** (**Scheme 6**) that should be metabolically suitable and accessible by using our developed synthetic strategy.

Scheme 6: Deuterium labeled MeCLA.



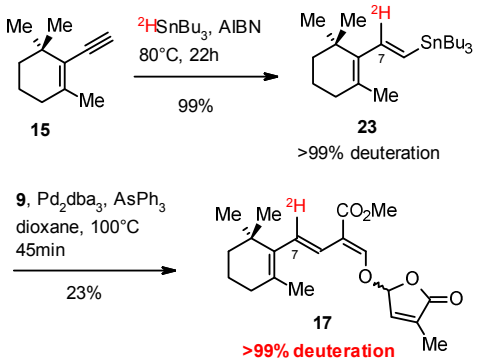
MeCLA (**18**) deuterated at the C10-position was synthesized as outlined in **Scheme 7**. Deutero methyl propynoate (**19**, 98% deuteration) could be synthesized under basic phase-transfer conditions using catalytic amounts of tetrabutylammonium iodide (TBAI) in a dichloromethane/ D_2O mixture.[15] Following the same procedure, we obtained deuterated butenolide alcohol **20** (50% deuteration). Deuteration of the latter was necessary due to significant H/D-exchange at propynoate **19** when non-deuterated butenolide alcohol **12** was employed in the Michael reaction. The Michael addition gave (*E*)-olefin **21** in 63% yield with 92% C10-deuteration accompanied by 78% of C9-deuteration. Iodination of **21** furnished vinyl iodide **22** (91% C10-deuteration), that could be coupled with vinyl stannane **10** to give MeCLA **18** with 91% C10-deuteration as measured by ^{1}H-NMR.

Scheme 7.



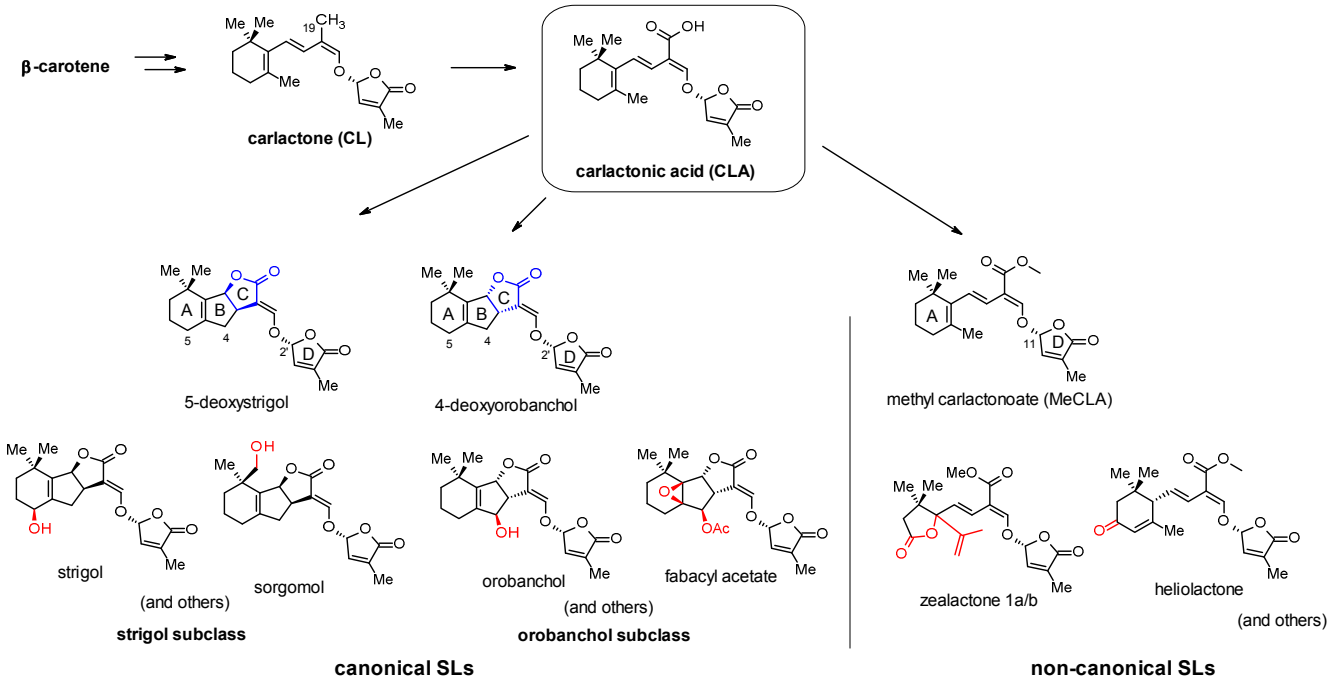
C7-deuterated MeCLA **17** could be obtained by using a deutero-stannylation of enyne **15** with deutero tributylstannane and subsequent Stille coupling with vinyl iodide **9** (**Scheme 8**). Both described approaches to deuterium-labeled MeCLA resulting in the deuterium label at C7 or C10 of the molecule should be applicable as well for other non-canonical strigolactones in a complementary fashion.

Scheme 8.



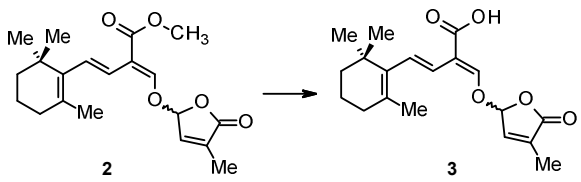
Carlactonic acid (CLA) biosynthetically derives from β-carotene that is oxidatively cleaved and cyclized to carlactone (CL), followed by further C19-oxidation delivering CLA (**Scheme 9**).[6] CLA has been shown to be the biosynthetic precursor for canonical strigolactones belonging to the strigol- and the orobanchol-subclass[6] and has also been hypothesized to be also the precursor for non-canonical strigolactones.[10]

Scheme 9: Pivotal role of carlactonic acid (CLA) in strigolactone biosynthesis.



We planned to synthesize carlactonic acid (CLA, **3**) from methyl carlactonoate (MeCLA, **2**) by ester cleavage. Basic aqueous conditions led, as expected, to decomposition of the material (**Table 2**, entry 1, 2). Neutral conditions using $(Bu_3Sn)_2O$[16] in toluene at room temperature gave low conversion with only traces of desired CLA (**3**) observed by LCMS analysis. The same conditions at 50 °C led to decomposition and again only traces of **3** were obtained as mixtures with various decomposition side products (entry 3). Enzymatic methyl ester hydrolyses were investigated using five different enzymes. In each case, acid **3** was detected in the reaction mixture but only traces of **3** accompanied by several unidentified side products were obtained. Furthermore, deactivation of the enzymes seemed to occur after initial partial conversion of MeCLA (**2**) to small amounts of desired CLA (**3**) (entries 4-8).

Table 2.



entry	conditions	conv./ yield of **3**
1	$Ba(OH)_2 \cdot 8H_2O$, MeOH rt, 18h	full decomp.

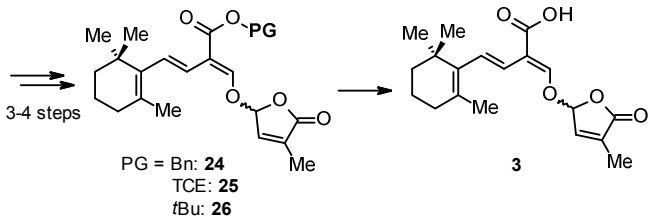
2	$LiOH{\cdot}H_2O$, THF/MeOH/H_2O rt, 18h	90% conv./ --
3	$(Bu_3Sn)_2O$, toluene, 24h rt or 50°C	full conv./ traces of **3**
4	*Candida rugosa lipase*[a]	80-90% conv./ traces of **3**
5	*Cal B lypozyme*[b]	" / "
6	*Lipolase 100L*[b]	" / "
7	*Novocor ADL*[b]	" / "
8	*Burkholderia cepacia lipase*[b]	" / "

a) toluene/phosphate buffer (aq, pH = 7, 0.05M), 24h;

b) cyclohexane/phosphate buffer (aq, pH = 7, 0.05M), 24h.

We thus decided to use other protecting groups instead of a methyl ester to synthesize acid **3**. In analogy to the developed synthesis of methyl ester **2**, the corresponding benzyl- (**24**), 2,2,2-trichloroethyl- (TCE) (**25**), and *tert*-butyl- (**26**) protected compounds were synthesized in three to four steps. We subsequently investigated potential protective group cleavage conditions as summarized in **Table 3**.

Table 3.



entry	PG	conditions	conv./ yield of **3**
1	Bn	10% Pd/C, H_2 (1 and 3 bar[b]), EtOAc, rt, 24h	full conv./ --
2	Bn	5% Pd/C, H_2, THF, rt, 24h	80-90% conv./ --
3	Bn	5% Pd/C, H_2, EtOH, rt, 24h	full conv./ --
4	Bn	5% Pd/C, cyclohexa-1,4-diene, EtOAc, rt, 24h	80-90% conv./--[a]
5	Bn	20% $Pd(OH)_2$/C, H_2, EtOAc, rt, 24h	80-90% conv./--[a]

6	Bn	Raney-Ni, H_2 (1 bar), EtOH/H_2O, rt, 48h	50% conv. / --
7	Bn	Raney-Ni, H_2 (10 bar)[b], EtOAc, rt	full conv./ --
8	TCE	Zn, AcOH, 0°C, 1h	full conv./ --
9	TCE	Zn, NH_4OAc, THF, rt, 1h	20-30% conv. /--
10	***t*Bu**	**TESOTf, 2,6-lutidine, DCM, 0°C, 3h**	**full conv./ 5%**

TCE = 2,2,2-trichloroethyl; a) hydrolysis of butenolide D-ring, **12** obtained as major side-product; b) H-cube® apparatus was used.

Hydrogenolyses of benzyl-compound **24** was investigated with 5-10% Pd/C in ethyl acetate, THF and ethanol as solvent. In addition, flow-conditions using an H-cube® apparatus at different H_2-pressures were probed. All of these conditions, however, led to decomposition of the material (entries 1-3, **Table 3**). Under transfer hydrogenolysis conditions using 1,4-cyclohexadiene as reductant, 80-90% conversion was obtained, with hydrolysed butenolide D-ring alcohol **12** as major side product (entry 4). A similar result was obtained when Pearlman's catalyst was employed (entry 5). Raney-nickel proved to be rather unreactive and led to decomposition at higher pressure (10 bar) under flow conditions (entries 6, 7). The attempted synthesis of a benzhydryl-analogue of **24** was not successful[17] and we decided to not further follow up a hydrogenolytic cleavage strategy due to the instability of the triene-moiety under such conditions. According to preliminary stability tests of **24** under common deprotection conditions such as tetrabutylammonium fluoride (TBAF), zinc/ acetic acid and TFA, we assumed that a 2,2,2-trichloroethyl (TCE)-ester could be a suitable protective group to synthesize acid **3** under mild reductive conditions. Unfortunately, also TCE-ester **25** could not be converted to **3**, when zinc/ acetic acid or zinc/ ammonium acetate[18] combinations were employed (entries 8, 9).

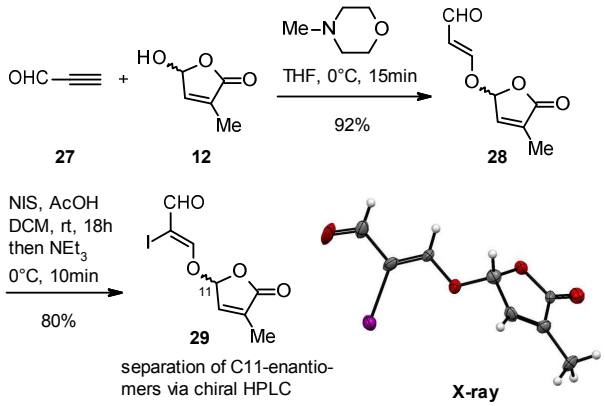
Akiyama, Yoneyama, Nomura and coworkers were able to synthesize carlactonic acid **3** by deprotection of the corresponding *tert*-butyl ester **26**.[10] They did not specify the yield for this transformation and described **26** as an unstable compound that was not isolated and directly submitted to deprotection

conditions using an excess of TES-triflate and 2,6-lutidine. In our hands, these conditions furnished **3** but resulted in a very low isolated yield of 5% (entry 10).

Reviewing the results of attempted deprotection reactions, methyl and especially *tert*-butyl esters could be cleaved, however, in only very low yield. The instability of compounds **2** and **26** presumably arises from the relative electron-rich triene moiety. Benzyl- and trichloroethyl-analogues **24** and **25** showed a higher hydrolytic stability, but also decomposed under reductive conditions and not even traces of deprotected acid **3** were detected. We thus modified our strategy aiming for an efficient synthesis of carlactonic acid **3** and investigated an approach without protecting groups. To test this strategy we focused on a free aldehyde-functionality that could be oxidized at a suitable stage to the carboxylic acid.

This modified route started with Michael-addition of butenolide alcohol **12** to propyne-aldehyde (**27**) (**Scheme 10**). Due to the increased electrophilicity of Michael-acceptor **27** compared to methyl propynoate (**11**) the reaction-time and -temperature were reduced. (*E*)-Olefin **28** was obtained in excellent yield and subjected to iodination under slightly modified conditions. Iodide **29** proved to be more labile in the presence of triethylamine and the iodoacetoxy-intermediate of **29** had to be treated with triethyl amine for short reaction times of 10 minutes at 0 °C in order to obtain 80% yield of desired vinyl iodide **29**. Racemic product *rac*-**29** was obtained as crystalline solid that in similarity to methyl ester **9** could be separated by HPLC on gram-scale to give pure C11-enantiomers (*R*)-**29** and (*S*)-**29**. Determination of stereochemistry by CD-analysis revealed the absolute configuration of both compounds.

Scheme 10: Protective-group free approach – synthesis of vinyl iodide **29**.

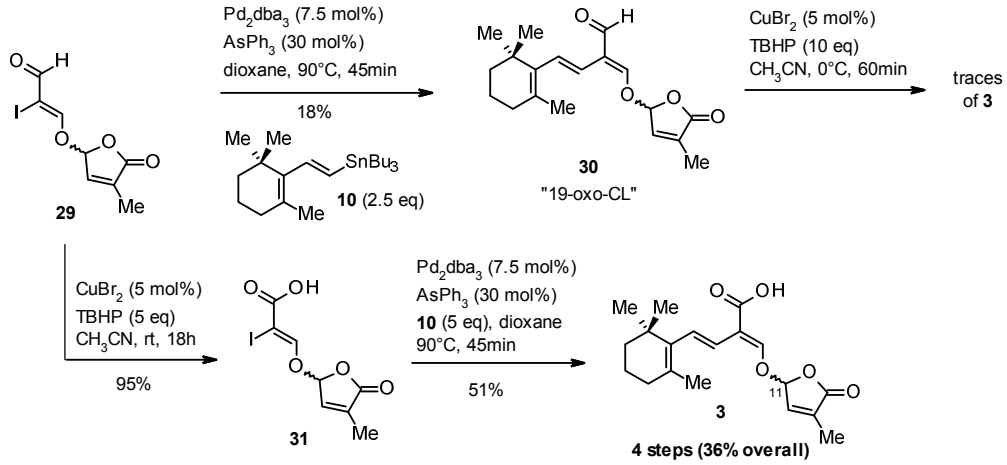


With aldehyde **29** in hand we envisaged two possibilities to synthesize carlactonic acid (**3**). On the one hand, by first performing a Stille cross-coupling with vinyl stannane **10** and oxidizing the aldehyde moiety under "mild" conditions; on the other hand, by oxidation of **29** and by cross-coupling of the obtained free carboxylic acid building block with stannane **10** to give **3**.

As shown in **Scheme 11**, vinyl iodide **29** could be coupled with stannane **10** to give **30** in moderate yield. Thereafter a variety of oxidation methods, including Pinnick-oxidation and Ag(I)-oxidation,[19] proved unsuitable. Oxidation methods described by Chakraborty and coworkers using *tert*-butyl hydroperoxide in combination with Fe(II)- or Cu(II)-salts[20] gave excellent results when aldehyde **28** was used as a model-system but resulted in only traces of carlactonic acid **3** when applied to aldehyde **30**. However, by this route we were able to synthesize "19-oxo-carlactone" **30** that has been hypothesized to be an intermediate in strigolactone biosynthesis but until now could not be synthesized successfully.[10] Our second option of inverting the Stille-coupling and the oxidation steps finally proved to be successful. Aldehyde **29** could be oxidized to acid **31** in excellent yield using *tert*-butyl hydroperoxide in the presence of a catalytic amount of $CuBr_2$. No racemization of the C11-stereocenter was observed when optically pure aldehydes (*R*)-**29** and (*S*)-**29** were submitted to these conditions. To our delight, Stille-coupling of the free carboxylic acid **31** with an excess of five equivalents of stannane **10** furnished carlactonic acid (**3**) in 51% yield. A lower amount of stannane **10** led to an increased protiodeiodination of vinyl iodide **30** and a lower yield of desired cross-coupling product **3**. Optically pure acids (*R*)-**31** and (*S*)-**31**, obtained from oxidation of (*R*)-**29** and (*S*)-**29**, applied within this cross-coupling, gave (*R*)- and (*S*)-carlactonic acid as stereochemically pure samples. This protecting-group-free route circumvents the

stability issues that we faced under a variety of tested deprotection conditions and gave access to carlactonic acid (**3**) in four linear steps with an overall yield of 36%. Carlactonic acid (**3**) shows an increased stability compared to methyl carlactonoate (**2**) and could be stored at -80 °C under argon for month without any significant decomposition.

Scheme 11: Synthesis of carlactonic acid (**3**) and 19-oxo-carlactone (**30**).



In summary, we have developed a synthetic access to natural products methyl carlactonoate, carlactonic acid and hypothesized 19-oxo-carlactone that should also be applicable to a broad variety of natural and non-natural non-canonical strigolactones. Furthermore, vinyl iodides as key-intermediates have been identified, allowing for the control of the C11-stereochemistry and two complementary approaches were found to introduce a deuterium-label. Key features of this synthetic strategy are a diastereoselective Michael-addition-iodination sequence and a Stille cross-coupling furnishing non-canonical strigolactones in a rapid and highly versatile fashion. These findings provide valuable tools for further biological investigations of strigolactones and may stimulate related syntheses of natural- as well as non-natural related bioactive compounds.

Experimental Section.

General Experimental Procedures

All chemicals and solvents were purchased from common suppliers and used as received. Chromatographic purifications were done on Rf-machine CombiFlash Rf 200i Teledyne ISCO equipped with standard silica columns or via flash column chromatography over silica gel (silica gel 60, 0.040-0.063 mm). Thin layer chromatography was performed on precoated TLC glass plates SIL G-25 with fluorescence indicator UV_{254}. Staining agents were either $KMnO_4$ (40 g of K_2CO_3 + 6g of $KMnO_4$ in 600 mL of water, then 5 mL of 10% NaOH added) or CAM (2 g $Ce(SO_4)_2$ + 60 g $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ in 360 mL of water, then 40 mL of H_2SO_4 conc. added) and subsequent heating of TLC plates treated with these staining solutions. ^1H and ^{13}C NMR spectra were recorder on Brucker spectrometer operating at 400 MHz and 100 MHz respectively unless otherwise stated. Chemical shifts are given in ppm. Tetramethyl silane was used as external reference. Following abbreviations describe the multiplets: s - singlet, d - doublet, t- triplet, q -quadruplet, m –multiplet, virt. - virtuell. Mass spectra were recorded on a High Resolution Mass Spectrometer (Q-Exactive, Orbitrap analyzer) from Thermofischer equipped with an electrospray source, (Polarity: positive mode, Capillary: 3.8 kV, Capillary temperature: 320°C, S-lens RF level: 55, Sheath gas flow rate: 40, Mass range: 100 to 1000 m/z) coupled to a 1200 Infinity series UPLC from Agilent: Solvent degasser, binary pump, heated column compartment and diode-array detector (DAD). DAD Wavelength range (nm): 190 to 400. Column: Waters Acquity UPLC BEH C18, 1.7 µm, 50 x 2.1 mm, Temp: 60 °C. Solvent Gradient: A = water + 5% MeOH + 0.05 % HCOOH, B= Acetonitrile + 0.05 % HCOOH. Infrared spectra were recorded on a Perkin Elmer UATR two FI-TR spectrometer. Melting points were measured on a Büchi Melting Point B-540 apparatus. Circular dichroism spectra were recorded on a Jasco J-815 apparatus.

***rac*-Methyl (*E*)-3-[(4-methyl-5-oxo-2H-furan-2-yl)oxy]prop-2-enoate (13):** To a solution of 2-hydroxy-4-methyl-2H-furan-5-one (**12**) (5.50 g, 48.0 mmol, 2.0 equiv.) in THF (50 mL) was added subsequently methyl prop-2-ynoate (**11**) (2.00 mL, 24.0 mmol, 1.0 equiv.) and 4-methylmorpholine (1.90 g, 19.0 mmol, 0.8 equiv.) at 0 °C. The clear orange solution was allowed to warm to ambient

temperature and was stirred for 18 h. An aqueous saturated solution of NH_4Cl (100 mL) was added, the mixture was extracted with diethyl ether (3 x 100 mL), combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, cyclohexane/ ethyl acetate = 2/1) gave the title compound as white solid (3.64 g, 18.4 mmol, 77%). R_f = 0.30 (cyclohexane/ ethyl acetate = 2/1); mp = 67-69 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.47 - 7.63 (m, 1 H), 7.55 (d, *J*=12.5 Hz, 1 H), 6.87 - 6.95 (m, 1 H), 6.04 - 6.14 (m, 1 H), 5.48 - 5.62 (m, 1 H), 3.66 - 3.75 (m, 3 H), 1.98 - 2.04 (m, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 170.4, 166.9, 157.7, 141.0, 135.4, 102.2, 99.2, 51.4, 10.6; HRMS: calc. for $C_9H_{11}O_5$ $[M+H]^+$: 199.0600, found: 199.0603; IR (cm^{-1}): 1778, 1712, 1651, 1631, 1437, 1367, 1326, 1289, 1171, 1131, 1095, 999, 952, 861, 846.

***rac-/* (*R*)-/ (*S*)- Methyl (*Z*)-2-iodo-3-[(4-methyl-5-oxo-2H-furan-2-yl)oxy]prop-2-enoate (9):** To a solution of **13** (1.00 g, 5.05 mmol, 1.00 equiv.) obtained from above in dichloromethane (10 mL) was added N-iodosuccinimide (1.59 g, 6.86 mmol, 1.36 equiv.) and glacial acetic acid (520 µL, 9.08 mmol, 1.80 equiv.) subsequently at room temperature. The red suspension was stirred for 8 h, afterwards further N-iodosuccinimide (0.80 g, 3.43 mmol, 0.68 equiv.) and glacial acetic acid (260 µL, 4.54 mmol, 0.90 equiv.) was added and the mixture was further stirred for 18 h until no starting material could be detected anymore by NMR-analysis. Triethylamine (2.28 mL, 16.3 mmol, 3.24 equiv.) was added and the dark solution was stirred for 6 h. An aqueous saturated solution of NH_4Cl (30 mL) and dichloromethane (20 mL) was added, the mixture was extracted with dichloromethane (3 x 30 mL), combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, cyclohexane/ ethyl acetate = 2/1) gave the title compound **9a/b** as white solid (1.41 g, 4.35 mmol, 86%). R_f = 0.30 (cyclohexane/ ethyl acetate = 2/1); mp = 126-128 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.96 (s, 1 H), 7.00 (s, 1 H), 6.26 (s, 1 H), 3.83 (s, 3 H), 2.05 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 170.1, 163.6, 158.2, 141.0, 135.9, 100.0, 70.5, 53.3, 10.8; HRMS: calc. for $C_9H_{10}IO_5$ $[M+H]^+$: 324.9567, found: 324.9567; IR (cm^{-1}): 1783, 1718, 1624, 1434, 1364, 1267, 1175, 1074, 1000, 955, 753. X-ray analysis was performed for racemic *rac*-**9**. Separation of enantiomers (*R*)-**9** and (*S*)-**9** via chiral HPLC: Daicel CHIRALPAK ® IF, Hept/EtOH = 70/30; *R*-stereoisomer (*R*)-**9**:

R_t = 5.32 min; $[\alpha]_D^{20}$ = +69.1° (c = 1.28, $CHCl_3$, 20 °C), stereochemical assignment: CD-analysis and *Orobanche cumana* germination assay; *S*-stereoisomer (*S*)-**9**: R_t = 8.61 min; $[\alpha]_D^{20}$ = –74.5° (c = 1.07, $CHCl_3$, 20 °C), stereochemical assignment: CD-analysis and *Orobanche cumana* germination assay. For further details see supporting information.

Methyl-(*Z*)-2-bromo-3-[(4-methyl-5-oxo-2H-furan-2-yl)oxy]prop-2-enoate (16): To a solution of **13** (100 mg, 505 µmol, 1.00 equiv.) in dichloromethane (2.5 mL) was added N-bromosuccinimide (122 mg, 686 µmol, 1.36 equiv.) and glacial acetic acid (52.0 µL, 908 µmol, 1.80 equiv.) subsequently at room temperature. The colorless suspension was stirred for 24 h, afterwards further N-bromosuccinimide (122 mg, 686 µmol, 1.36 equiv.) and glacial acetic acid (52.0 µL, 908 µmol, 1.80 equiv.) subsequently were added at room temperature. The colorless suspension was stirred 24 h until no starting material could be detected anymore by NMR-analysis. Triethylamine (228 µL, 1.64 mmol, 3.24 equiv.) was added and the solution was stirred for 6 h. An aqueous saturated solution of NH_4Cl (7 mL) and dichloromethane (10 mL) was added, the mixture was extracted with dichloromethane (3 x 10 mL), combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, cyclohexane/ ethyl acetate = 2/1) gave the title compound as yellowish solid (48.0 mg, 173 µmol, 34%). R_f = 0.24 (cyclohexane/ ethyl acetate = 2/1); mp = 104-106 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.06 (s, 1 H), 7.03 (s, 1 H), 6.25 (s, 1 H), 3.85 (s, 3 H), 2.06 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 170.0, 163.0, 153.3, 140.9, 135.9, 100.1, 53.0, 26.9, 10.7; HRMS: calc. for $C_9H_{10}{}^{79}BrO_5$ $[M+H]^+$: 276.9706, found: 276.9709; IR (cm^{-1}): 1784, 1723, 1638, 1437, 1365, 1278, 1178, 1081, 1051, 1001, 957, 754.

Tributyl-[(*E*)-2-(2,6,6-trimethylcyclohexen-1-yl)vinyl]stannane (10): In a 10 mL microwave tube was added 2-ethynyl-1,3,3-trimethyl-cyclohexene (**15**)[14] (593 mg, 4.00 mmol, 1.0 equiv.), tributyl stannane (1.06 mL, 4.00 mmol, 1.0 equiv.) and AIBN (67.0 mg, 400 µmol, 0.1 equiv.) under argon. The vial was sealed and the mixture was stirred and heated to 80 °C for 24 h. The solution was allowed to cool to rt and was filtered over Celite (wash with cyclohexane, 15 mL). The solvent was removed *in*

vacuo to give the title compound 1.80 g, 4.00 mmol, 99%) as colorless oil. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 6.36 (d, *J* = 19.4 Hz, 1 H), 5.87 (d, *J* = 19.4 Hz, 1 H), 1.97 (virt. t, *J* = 6.2 Hz, 2 H), 1.67 (d, *J* = 0.7 Hz, 3 H), 1.62-1.57 (m, 2 H), 1.56-1.50 (m, 6 H), 1.45-1.42 (m, 2 H), 1.32 (sext., *J* = 7.3 Hz, 6 H), 1.00 (s, 6 H), 0.93-0.88 (m, 6 H), 0.89 (t, *J* = 7.3 Hz, 9 H); ^{13}C NMR (101 MHz, CD_2Cl_2) δ ppm 146.5, 141.9, 132.9, 127.9, 40.0, 34.2, 33.1, 29.8, 29.1, 27.8, 21.9, 19.9, 14.1, 10.1; IR (cm^{-1}): 2956, 2924, 2870, 2853, 1457, 991, 689, 664, 592, 504.

***rac*-/ (*R*)-/ (*S*)-Methyl (*E*,2*E*)-2-[(4-methyl-5-oxo-2H-furan-2-yl)oxymethylene]-4-(2,6,6-trimethylcyclohexen-1-yl)but-3-enoate (2, methyl carlactonoate, Me-CLA):** To a solution of vinyl iodide *rac*-**9** (20.0 mg, 61.7 μmol, 1.00 equiv.) and triphenylarsane (5.7 mg, 18.5 μmol, 0.30 equiv.) in dioxane (620 μL) was added vinylstannane **10** (67.8 mg, 154 μmol, 2.50 equiv.) under argon atmosphere. The solution was degassed by bubbling argon through the solution for 10 min. Pd_2dba_3 (4.2 mg, 4.63 μmol, 0.075 equiv.) was added, the reaction vial was sealed and heated to 90 °C for 45 min. The clear yellow mixture was allowed to cool to rt and was filtered over Celite (wash with CyH/EtOAc = 2/1, 20 mL). The solvent was removed *in vacuo* and the crude was purified by flash column chromatography (SiO_2, cyclohexane/ ethyl acetate = 4/1). The title compound (Me-CLA) was obtained as colorless oil (16.0 mg, 46.2 μmol, 75%). Performing this procedure using enantiomerically pure vinyliodides (*R*)-**9** / (*S*)-**9** obtained as described above delivered (*R*)-Me-CLA ((*R*)-**2**) and (*S*)-Me-CLA ((*S*)-**2)** in similar yields. R_f = 0.29 (cyclohexane/ ethyl acetate = 2/1); ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 7.51 (s, 1 H), 6.98 - 6.96 (m, 1 H), 6.79 (d, *J* = 16.5 Hz, 1 H), 6.17 – 6.15 (m, 1 H), 6.08 (d, *J* = 16.5 Hz, 1 H), 3.73 (s, 3 H), 2.00 (virt. t, *J* = 6.2 Hz, 2 H), 1.98 (t, *J* = 1.5 Hz, 3 H), 1.69 (d, *J* = 0.7 Hz, 3 H), 1.62 – 1.57 (m, 2 H), 1.46 – 1.43 (m, 2 H), 0.99 (s, 6 H); ^{13}C NMR (101 MHz, CD_2Cl_2) δ ppm 171.1, 167.5, 151.9, 141.9, 138.8, 135.9, 133.0, 129.7, 122.3, 113.4, 101.1, 52.0, 40.1, 34.6, 33.4, 29.2, 29.1, 21.9, 19.8, 11.0; HRMS: calc. for $C_{20}H_{27}O_5$ $[M+H]^+$: 347.1853, found: 347.1854; IR (cm^{-1}): 2930, 2869, 1769, 1603, 1438, 1345, 1249, 1206, 1091, 1010, 951, 864, 768, 746; $[\alpha]_D^{20}$ ((*R*)-Me-CLA, (*R*)-**2**)

= +9.9° (c = 0.53, CH_2Cl_2, 20 °C), $[\alpha]_D^{20}$ ((*S*)-Me-CLA, (*S*)-**2**) = –30.4° (c = 0.57, CH_2Cl_2, 20 °C); see also supporting information.

Methyl 3-deuterioprop-2-ynoate (19)[15]: In a round bottom flask K_2CO_3 (59.5 mg, 431 μmol, 0.018 equiv.) and tetrabutylammonium iodide (106 mg, 431 μmol, 0.012 equiv.) were placed as solids. Dichloromethane (dry, 5.00 mL), deuterium oxide (5.00 mL) and methyl prop-2-ynoate (**11**) (2.00 mL, 23.9 mmol, 1.00 equiv.) were added subsequently and the clear yellowish suspension was stirred for 18 h at rt. The layers were separated, the aqueous layer was extracted with DCM (2 x 5.00 mL), combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. 2nd cycle: The obtained yellowish oil was dissolved in DCM (dry, 5.00 mL), deuterium oxide (5.00 mL), K_2CO_3 (59.5 mg) and tetrabutylammonium iodide (106 mg) were added and the mixture was stirred at rt for 5 h. The layers were separated, the aqueous layer was extracted with DCM (2 x 5.00 mL), combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the title compound as a yellowish oil (97.5% deuteration, 950 mg, 11.2 mmol, 47%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.81 (s, 3 H).

2-Deuteriooxy-4-methyl-2H-furan-5-one (20): In a round bottom flask K_2CO_3 (55.0 mg, 390 μmol, 0.018 equiv.) and tetrabutylammonium iodide (97.0 mg, 260 μmol, 0.012 equiv.) were placed as solids. Dichloromethane (dry, 5.00 mL), deuterium oxide (5.00 mL) and 2-hydroxy-4-methyl-2H-furan-5-one (2.50 g, 22.0 mmol, 1.00 equiv.) were added subsequently and the clear yellow suspension was stirred for 48 h at rt. The layers were separated, the aqueous layer was extracted with DCM (2 x 5.00 mL), combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. 2nd cycle: The obtained yellow solid (35% deuteration as judged by ^{1}H-NMR) was dissolved in DCM (dry, 5.00 mL), deuterium oxide (5.00 mL), K_2CO_3 (55.0 mg) and tetrabutylammonium iodide (97.0 mg) were added and the mixture was stirred at rt for 48 h. The layers were separated, the aqueous layer was extracted with DCM (2 x 5.00 mL), combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the title compound as a yellow solid (50% deuteration, 400 mg, 3.49 mmol, 16%). ^{1}H

NMR (400 MHz, DMSO-*d*6) δ ppm 7.68 (broad s, 0.50 H), 7.06 (s, 1 H), 6.15 (s, 1 H), 1.81 (s, 3 H); HRMS: calc. for $C_5{}^2HH_6O_3$ $[M+H]^+$: 116.0452, found: 116.0453.

Methyl (*E*)-3-deuterio-3-[(4-methyl-5-oxo-2H-furan-2-yl)oxy]prop-2-enoate (21): To a solution of 2-deuteriooxy-4-methyl-2H-furan-5-one (**20**) (50.0 mg, 434 μmol, 1.0 equiv.) in THF (1.00 mL) was added methyl 3-deuterioprop-2-ynoate (**19**) (148 mg, 1.73 mmol, 4.0 equiv.) and 4-methylmorpholine (35.0 mg, 347 μmol, 0.8 equiv.) subsequently at 0 °C. The clear orange solution was allowed to warm to ambient temperature and was stirred for 24 h. An aqueous saturated solution of NH_4Cl (5.0 mL) was added, the mixture was extracted with diethyl ether (3 x 7.0 mL), combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, cyclohexane/ ethyl acetate = 2/1) gave the title compound as yellow oil (54.0 mg, 270 μmol, 62%). 92% β-deuteration, accompanied by 78% α-deuteration was obtained as judged by ^{1}H-NMR. R_f = 0.30 (cyclohexane/ ethyl acetate = 2/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.56 (s, 0.08 H), 6.93 (s, 1 H), 6.11 (s, 1 H), 5.88 (s, 0.15 H), 3.74 (s, 3 H), 2.02 (s, 3 H); HRMS: calc. for $C_9{}^2H_2H_9O_5$ $[M+H]^+$: 201.0726, found: 201.0727.

Methyl (*Z*)-3-deuterio-2-iodo-3-[(4-methyl-5-oxo-2H-furan-2-yl)oxy]prop-2-enoate (22): To a solution of **21** (100 mg, 500 μmol, 1.00 equiv.) obtained from above in dichloromethane (5.00 mL) was added N-iodosuccinimide (158 mg, 679 μmol, 1.36 equiv.) and glacial acetic acid (51.0 μL, 899 μmol, 1.80 equiv.) subsequently at room temperature. The red suspension was stirred for 18 h, afterwards further N-iodosuccinimide (79.0 mg, 340 μmol, 0.68 equiv.) and glacial acetic acid (25.0 μL, 450 μmol, 0.90 equiv.) was added and the mixture was further stirred for 6 h until no starting material could be detected anymore by NMR-analysis. Triethylamine (226 μL, 1.62 mmol, 3.24 equiv.) was added and the dark solution was stirred for 14 h. An aqueous saturated solution of NH_4Cl (7.0 mL) and dichloromethane (7.0 mL) was added, the mixture was extracted with dichloromethane (2 x 10 mL), combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, cyclohexane/ ethyl acetate = 2/1) gave the title compound as white solid

(82.6 mg, 255 μmol, 51%). 91% deuteration was obtained as judged by ^{1}H-NMR. R_f = 0.30 (cyclohexane/ ethyl acetate = 2/1); ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 7.93 (s, 0.09 H), 7.01 (s, 1 H), 6.27 (s, 1 H), 3.78 (s, 3 H), 2.00 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 170.1, 163.6, 158.2, 141.0, 135.9, 100.0, 70.3, 53.3, 10.8; HRMS: calc. for $C_9{}^2HH_9IO_5$ $[M+H]^+$: 325.9630, found: 325.9629.

***rac*-Methyl (*E*,2*E*)-2-[deuterio-[(4-methyl-5-oxo-2H-furan-2-yl)oxy]methylene]-4-(2,6,6-trimethylcyclohexen-1-yl)but-3-enoate (18, deutero-Me-CLA):** To a solution of deutero vinyl iodide **22** (30.0 mg, 92.3 μmol, 1.00 equiv.) and triphenylarsane (11.3 mg, 36.9 μmol, 0.40 equiv.) in dioxane (400 μL) was added vinylstannane **10** (122 mg, 277 μmol, 3.00 equiv.) under argon atmosphere. The solution was degassed by bubbling argon through the solution for 10 min. Pd_2dba_3 (8.50 mg, 9.23 μmol, 0.10 equiv.) was added, the reaction vial was sealed and heated to 100 °C for 45 min. The clear yellow mixture was allowed to cool to rt and was filtered over Celite (wash with cyclohexane/ ethyl acetate = 2/1, 10 mL). The solvent was removed *in vacuo* and the crude was purified by flash column chromatography (SiO_2, cyclohexane/ ethyl acetate = 4/1). The title compound (deuteron-Me-CLA) was obtained as colorless oil (14.0 mg, 40.3 μmol, 44%, 91% deuteration as judged by ^{1}H-NMR). R_f= 0.29 (CyH/EA = 2/1); ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 7.51 (s, 0.09 H), 6.97 - 6.95 (m, 1 H), 6.79 (d, *J* = 16.9 Hz, 1 H), 6.17 – 6.15 (m, 1 H), 6.08 (d, *J* = 16.9 Hz, 1 H), 3.73 (s, 3 H), 2.00 (virt. t, *J* = 5.9 Hz, 2 H), 1.99-1.97 (m, 3 H), 1.69 (d, *J* = 0.7 Hz, 3 H), 1.62 – 1.58 (m, 2 H), 1.47 – 1.43 (m, 2 H), 0.99 (s, 6 H); HRMS: calc. for $C_{20}{}^2HH_{26}O_5$ $[M+H]^+$: 348.1916, found: 348.1914.

Tributyl-[(*E*)-2-deuterio-2-(2,6,6-trimethylcyclohexen-1-yl)vinyl]stannane (23): In a 10 mL microwave tube was added 2-ethynyl-1,3,3-trimethyl-cyclohexene (**15**)[14] (222 mg, 1.50 mmol, 1.0 equiv.), tributyl(deuterio)stannane (400 μL, 1.50 mmol, 1.0 equiv.) and AIBN (25.1 mg, 150 μmol, 0.1 equiv.) under argon. The vial was sealed and the mixture was stirred and heated to 80 °C for 22 h. The solution was allowed to cool to rt and was filtered over Celite (wash with cyclohexane, 15 mL). The solvent was removed *in vacuo* to give the title compound 660 mg, 1.50 mmol, 99%, deuteration >99% as judged by ^{1}H-NMR) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 6.13 (s, 1 H), 1.94 (virt. t, *J*

= 6.2 Hz, 2 H), 1.62 (s, 3 H), 1.52-1.49 (m, 2 H), 1.49-1.43 (m, 6 H), 1.36-1.31 (m, 2 H), 1.31 (sext., *J* = 7.7 Hz, 6 H), 0.98 (s, 6 H), 0.93-0.88 (m, 6 H), 0.89 (t, *J* = 7.3 Hz, 9 H); HRMS: calc. for $C_{23}{}^{2}HH_{44}{}^{120}Sn$ $[M+H]^+$: 442.2600, mass not found.

***rac*-Methyl (*E*,2*E*)-4-deuterio-2-[(4-methyl-5-oxo-2H-furan-2-yl)oxymethylene]-4-(2,6,6-trimethylcyclohexen-1-yl)but-3-enoate (17, deutero-Me-CLA):** To a solution of vinyl iodide *rac*-**9** (45.0 mg, 139 μmol, 1.00 equiv.) and triphenylarsane (17.0 mg, 55.5 μmol, 0.40 equiv.) in dioxane (1.50 mL) was added deutero-vinylstannane **23** (183 mg, 417 μmol, 3.00 equiv.) under argon atmosphere. The solution was degassed by bubbling argon through the solution for 10 min. Pd_2dba_3 (12.7 mg, 13.9 μmol, 0.10 equiv.) was added, the reaction vial was sealed and heated to 100 °C for 60 min. The clear yellow mixture was allowed to cool to rt and was filtered over Celite (wash with cyclohexane/ ethyl acetate = 2/1, 20 mL). The solvent was removed *in vacuo* and the crude was purified by flash column chromatography (SiO_2, cyclohexane/ ethyl acetate = 4/1). The title compound (deutero-Me-CLA) was obtained as colorless oil (11.0 mg, 31.7 μmol, 23%, >99% deuteration as judged by ^{1}H-NMR). R_f = 0.29 (cyclohexane/ ethyl acetate = 2/1); ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 7.51 (s, 1 H), 6.97 - 6.96 (m, 1 H), 6.17 – 6.15 (m, 1 H), 6.08 (bs, 1 H), 3.73 (s, 3 H), 2.00 (virt. t, *J* = 6.2 Hz, 2 H), 1.98 (t, *J* = 1.5 Hz, 3 H), 1.70 (s, 3 H), 1.62 – 1.58 (m, 2 H), 1.47 – 1.44 (m, 2 H), 0.99 (s, 6 H); HRMS: calc. for $C_{20}{}^{2}HH_{26}O_5$ $[M+H]^+$: 348.1916, found: 348.1919.

***rac*-Benzyl (*E*,2*E*)-2-[(4-methyl-5-oxo-2H-furan-2-yl)oxymethylene]-4-(2,6,6-trimethylcyclohexen-1-yl)but-3-enoate (24, benzyl carlactonate, Bn-CLA):** To a solution of 2-hydroxy-4-methyl-2H-furan-5-one (**12**) (2.07 g, 18.1 mmol, 2.0 equiv.) in THF (20.0 mL) was added subsequently benzyl prop-2-ynoate (1.45 g, 9.05 mmol, 1.0 equiv.) and 4-methylmorpholine (733 mg, 7.24 mmol, 0.8 equiv.) at 0 °C. The clear yellowish solution was allowed to warm to ambient temperature and was stirred for 24 h. An aqueous saturated solution of NH_4Cl (25 mL) and dichloromethane (20 mL) was added. After separation the aqueous layer was extracted with dichloromethane (3 x 30 mL), combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, cyclohexane/ ethyl acetate = 2/1) gave the Michael addition product as colorless oil (R_f = 0.25

(cyclohexane/ ethyl acetate = 2/1), 1.80 g, 6.56 mmol). The obtained compound (1.80 g, 6.56 mmol, 1.0 equiv.) was dissolved in dichloromethane (30.0 mL), N-iodosuccinimide (2.07 g, 8.93 mmol, 1.36 equiv.) and glacial acetic acid (676 µL, 11.8 mmol, 1.80 equiv.) were added subsequently at room temperature. The red suspension was stirred for 8 h, afterwards further N-iodosuccinimide (1.04 g, 4.47 mmol, 0.68 equiv.) and glacial acetic acid (338 µL, 5.90 mmol, 0.90 equiv.) was added and the mixture was further stirred for 18 h until no starting material could be detected anymore by NMR-analysis. Triethylamine (2.96 mL, 21.3 mmol, 3.24 equiv.) was added and the dark solution was stirred for 6 h. An aqueous saturated solution of NH_4Cl (30 mL) and dichloromethane (20 mL) was added, layers were separated, the aqueous layer was extracted with dichloromethane (3 x 30 mL), combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, cyclohexane/ ethyl acetate = 4/1 to 2/1) gave the respective vinyl iodide compound as yellowish solid (1.71 g, 4.27 mmol, 47%). R_f = 0.33 (cyclohexane/ ethyl acetate = 2/1); mp = 85-87 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.97 (s, 1 H), 7.37 - 7.44 (m, 5 H), 6.95 - 7.04 (m, 1 H), 6.21 - 6.27 (m, 1 H), 5.27 (d, *J* = 15.0 Hz, 1 H), 5.23 (d, *J* = 15.0 Hz, 1 H), 2.01 - 2.06 (m, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 170.0, 163.0, 158.5, 140.9, 135.9, 135.4, 128.6, 128.4, 128.2, 100.0, 70.9, 68.0, 10.7; HRMS: calc. for $C_{15}H_{14}IO_5$ $[M+H]^+$: 400.9881, found: 400.9880; IR (cm^{-1}): 1783, 1711, 1624, 1374, 1361, 1259, 1172, 1040, 1000, 954, 750. To a solution of vinyl iodide obtained from above (200 mg, 500 µmol, 1.00 equiv.) and triphenylarsane (45.9 mg, 150 µmol, 0.30 equiv.) in dioxane (5.00 mL) was added vinylstannane **10** (549 mg, 1.25 mmol, 2.50 equiv.) under argon atmosphere. The solution was degassed by bubbling argon through the solution for 10 min. Pd_2dba_3 (34.3 mg, 37.5 µmol, 0.075 equiv.) was added, the reaction vial was sealed and heated to 90 °C for 50 min. The clear yellow mixture was allowed to cool to rt and was filtered over Celite (wash with cyclohexane/ ethyl acetate = 2/1, 20 mL). The solvent was removed *in vacuo* and the crude was purified by flash column chromatography (SiO_2, cyclohexane/ ethyl acetate = 4/1). The title compound **24** (Bn-CLA) was obtained as colorless oil (93.0 mg, 220 µmol, 44%). R_f = 0.46 (cyclohexane/ ethyl acetate = 2/1); ^{1}H

NMR (400 MHz, CD_2Cl_2) δ ppm 7.55 (s, 1 H), 7.40 – 7.32 (m, 5 H), 6.96 - 6.94 (m, 1 H), 6.78 (d, *J* = 16.5 Hz, 1 H), 6.16 – 6.15 (m, 1 H), 6.09 (d, *J* = 16.5 Hz, 1 H), 5.21 (d, *J* = 14.7 Hz, 1 H), 5.18 (d, *J* = 16.5 Hz, 1 H), 1.99 (virt. t, *J* = 6.2 Hz, 2 H), 1.97 (t, *J* = 1.5 Hz, 3 H), 1.68 (s, 3 H), 1.63 – 1.56 (m, 2 H), 1.46 – 1.42 (m, 2 H), 0.97 (s, 6 H); ^{13}C NMR (101 MHz, CD_2Cl_2) δ ppm 171.1, 166.9, 152.3, 141.9, 138.8, 136.9, 135.9, 133.1, 129.7, 129.1, 128.7, 122.3, 113.5, 101.2, 67.6, 66.7, 40.1, 34.6, 33.4, 29.1, 29.1, 21.9, 19.8, 11.0; HRMS: calc. for $C_{26}H_{31}O_5$ $[M+H]^+$: 423.2166, found: 423.2165; IR (cm^{-1}): 2957, 2928, 2866, 1784, 1713, 1456, 1351, 1249, 1186, 1112, 1015, 952, 864, 753.

***rac*-2,2,2-trichloroethyl (*E*,2*E*)-2-[(4-methyl-5-oxo-2H-furan-2-yl)oxymethylene]-4-(2,6,6-trimethylcyclohexen-1-yl)but-3-enoate (25, trichloroethyl carlactonoate, TCE-CLA):** To a solution of 2-hydroxy-4-methyl-2H-furan-5-one (**12**) (170 mg, 1.49 mmol, 2.0 equiv.) in THF (2.00 mL) was added subsequently 2,2,2-trichloroethyl prop-2-ynoate (**11**) (150 mg, 745 μmol, 1.0 equiv.) and 4-methylmorpholine (66.0 μL, 596 μmol, 0.8 equiv.) at 0 °C. The clear yellowish solution was allowed to warm to ambient temperature and was stirred for 18 h. An aqueous saturated solution of NH_4Cl (25 mL) and dichloromethane (20 mL) was added. After separation the aqueous layer was extracted with dichloromethane (3 x 30 mL), combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, cyclohexane/ ethyl acetate = 2/1) gave the Michael addition product as colorless oil (R_f = 0.31 (cyclohexane/ ethyl acetate = 2/1), 96.0 mg, 304 μmol). The obtained compound (96.0 mg, 304 μmol, 1.0 equiv.) was dissolved in dichloromethane (2.90 mL), N-iodosuccinimide (90.0 mg, 388 μmol, 1.36 equiv.) and glacial acetic acid (29.4 μL, 514 μmol, 1.80 equiv.) were added subsequently at room temperature. The red suspension was stirred for 8 h, afterwards further N-iodosuccinimide (90.0 mg, 388 μmol, 1.36 equiv.) and glacial acetic acid (29.4 μL, 514 μmol, 1.80 equiv.) was added and the mixture was further stirred for 18 h until no starting material could be detected anymore by NMR-analysis. Triethylamine (129 μL, 924 μmol, 3.24 equiv.) was added and the dark solution was stirred for 6 h. An aqueous saturated solution of NH_4Cl (30 mL) and dichloromethane (20 mL) was added, layers were separated, the aqueous layer was extracted with

dichloromethane (3 x 30 mL), combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, cyclohexane/ ethyl acetate = 4/1 to 2/1) gave the respective vinyl iodide as yellow oil (45.0 mg, 102 μmol, 14%). R_f = 0.41 (cyclohexane/ ethyl acetate = 2/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.07 (s, 1 H), 7.04 - 7.02 (m, 1 H), 6.31 – 6.30 (m, 1 H), 4.88 (d, *J* = 11.7 Hz, 1 H), 4.83 (d, *J* = 11.7 Hz, 1 H), 2.06 (virt. t, *J* = 1.5 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 169.9, 161.6, 159.7, 140.8, 136.1, 100.1, 94.7, 75.3, 68.9, 10.8; HRMS: calc. for $C_{10}H_9Cl_3IO_5$ $[M+H]^+$: 440.8555, found: 440.8553; IR (cm^{-1}): 1787, 1731, 1621, 1370, 1246, 1175, 1094, 1043, 1007, 956, 744, 712. To a solution of vinyl iodide obtained from above (25.0 mg, 56.6 μmol, 1.00 equiv.) and triphenylarsane (5.2 mg, 17.0 μmol, 0.30 equiv.) in dioxane (1.00 mL) was added vinylstannane **10** (74.6 mg, 170 μmol, 2.50 equiv.) under argon atmosphere. The solution was degassed by bubbling argon through the solution for 10 min. Pd_2dba_3 (3.9 mg, 4.25 μmol, 0.075 equiv.) was added, the reaction vial was sealed and heated to 90 °C for 30 min. The clear yellow mixture was allowed to cool to rt and was filtered over Celite (wash with cyclohexane/ ethyl acetate = 2/1, 15 mL). The solvent was removed *in vacuo* and the crude was purified by flash column chromatography (SiO_2, cyclohexane/ ethyl acetate = 4/1). The title compound **25** (TCE-CLA) was obtained as colorless oil (15.0 mg, 32.3 μmol, 57%). R_f = 0.37 (cyclohexane/ ethyl acetate = 4/1); ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 7.65 (s, 1 H), 6.99 - 6.97 (m, 1 H), 6.84 (d, *J* = 16.5 Hz, 1 H), 6.22 – 6.21 (m, 1 H), 6.12 (d, *J* = 16.5 Hz, 1 H), 4.87 (d, *J* = 11.7 Hz, 1 H), 4.83 (d, *J* = 16.5 Hz, 1 H), 2.01 (virt. t, *J* = 6.5 Hz, 2 H), 1.99 (t, *J* = 1.5 Hz, 3 H), 1.71 (s, 3 H), 1.64 – 1.58 (m, 2 H), 1.48 – 1.45 (m, 2 H), 1.01 (s, 6 H); ^{13}C NMR (101 MHz, CD_2Cl_2) δ ppm 170.7, 165.5, 153.2, 141.8, 136.2, 133.7, 130.0, 121.7, 112.5, 101.2, 95.9, 74.6, 40.1, 34.6, 33.5, 29.2, 27.5, 21.9, 19.8, 11.0; HRMS: calc. for $C_{21}H_{26}Cl_3O_5$ $[M+H]^+$: 463.0840, found: 463.0842; IR (cm^{-1}): 2957, 2929, 2867, 1787, 1728, 1606, 1449, 1371, 1241, 1190, 1107, 1048, 1014, 954, 716.

***rac-tert*-Butyl (*E*,2*E*)-2-[(4-methyl-5-oxo-2H-furan-2-yl)oxymethylene]-4-(2,6,6-trimethylcyclohexen-1-yl)but-3-enoate (26, *tert*-butyl carlactonate, *t*Bu-CLA):** To a solution of 2-

hydroxy-4-methyl-2H-furan-5-one (**12**) (317 mg, 2.78 mmol, 2.0 equiv.) in THF (2.8 mL) was added subsequently *tert*-butyl prop-2-ynoate (**11**) (176 mg, 1.39 mmol, 1.0 equiv.) and 4-methylmorpholine (113 mg, 1.11 mmol, 0.8 equiv.) at 0 °C. The clear yellowish solution was allowed to warm to ambient temperature and was stirred for 22 h. An aqueous saturated solution of NH_4Cl (25 mL) and dichloromethane (20 mL) was added. After separation the aqueous layer was extracted with dichloromethane (3 x 30 mL), combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, cyclohexane/ ethyl acetate = 2/1) gave the Michael addition product as colorless oil (R_f = 0.35 (cyclohexane/ ethyl acetate = 2/1), 200 mg, 832 µmol). The obtained compound (200 mg, 832 µmol, 1.0 equiv.) was dissolved in dichloromethane (2.8 mL), N-iodosuccinimide (262 mg, 1.17 mmol, 1.40 equiv.) and glacial acetic acid (86 µL, 1.50 mmol, 1.80 equiv.) were added subsequently at room temperature. The red suspension was stirred for 8 h until no starting material could be detected anymore by NMR-analysis. Triethylamine (376 µL, 2.70 mmol, 3.24 equiv.) was added and the dark solution was stirred for 18 h. Further amount of triethylamine (376 µL, 2.70 mmol, 3.24 equiv.) was added and the dark solution was stirred for another 24 h. An aqueous saturated solution of NH_4Cl (20 mL) and dichloromethane (20 mL) was added, layers were separated, the aqueous layer was extracted with dichloromethane (3 x 30 mL), combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, cyclohexane/ ethyl acetate = 2/1) gave the respective vinyl iodide as yellowish oil (231 mg, 631 µmol, 45%). R_f= 0.36 (cyclohexane/ ethyl acetate = 2/1); ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 7.82 (s, 1 H), 7.00 – 6.99 (m, 1 H), 6.25 - 6.24 (m, 1 H), 1.98 (s, 3 H), 1.47 (s, 9 H); ^{13}C NMR (101 MHz, CD_2Cl_2) δ ppm 170.8, 162.4, 158.3, 141.7, 136.2, 100.9, 83.3, 74.4, 28.3, 11.0; HRMS: calc. for $C_{12}H_{16}IO_5$ $[M+H]^+$: 367.0037, found: 367.0039; IR (cm^{-1}): 2979, 1783, 1705, 1652, 1633, 1368, 1331, 1209, 1155, 1125, 1051, 1021, 978, 953, 847. To a solution of vinyl iodide obtained from above (50.0 mg, 137 µmol, 1.00 equiv.) and triphenylarsane (12.5 mg, 41.0 µmol, 0.30 equiv.) in dioxane (1.40 mL) was added vinylstannane **10** (180 mg, 410 µmol, 3.00 equiv.) under argon atmosphere. The solution was degassed

by bubbling argon through the solution for 10 min. Pd_2dba_3 (9.4 mg, 10.2 μmol, 0.075 equiv.) was added, the reaction vial was sealed and heated to 90 °C for 45 min. The clear yellow mixture was allowed to cool to rt and was filtered over Celite (wash with cyclohexane/ ethyl acetate = 2/1, 20 mL). The solvent was removed *in vacuo* and the crude was purified by flash column chromatography (SiO_2, cyclohexane/ ethyl acetate = 4/1). The title compound **26** (*t*Bu-CLA) was obtained as colorless oil (25.0 mg, 64.4 μmol, 47%). R_f = 0.36 (cyclohexane/ ethyl acetate = 4/1); ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 7.41 (s, 1 H), 6.96 - 6.95 (m, 1 H), 6.72 (d, *J* = 16.5 Hz, 1 H), 6.15 – 6.14 (m, 1 H), 6.05 (d, *J* = 16.5 Hz, 1 H), 2.00 (virt. t, *J* = 6.2 Hz, 2 H), 1.97 (t, *J* = 1.5 Hz, 3 H), 1.70 (s, 3 H), 1.63 – 1.59 (m, 2 H), 1.49 (s, 9 H), 1.49 – 1.46 (m, 2 H), 0.99 (s, 6 H); ^{13}C NMR (101 MHz, CD_2Cl_2) δ ppm 171.2, 166.4, 151.2, 141.9, 139.0, 135.8, 132.5, 130.1, 122.7, 115.0, 101.1, 40.1, 34.6, 33.5, 29.21, 29.18, 28.6, 21.9, 19.9, 17.1, 11.0; HRMS: calc. for $C_{23}H_{33}O_5$ $[M+H]^+$: 389.2322, found: 389.2323; IR (cm^{-1}): 2959, 2931, 2817, 1780, 1710, 1622, 1451, 1369, 1340, 1253, 1160, 1122, 1095, 1015, 953, 864, 768, 699.

(*E*)-3-[(4-methyl-5-oxo-2H-furan-2-yl)oxy]prop-2-enal (28): To a solution of 2-hydroxy-4-methyl-2H-furan-5-one (**12**) (317 mg, 2.78 mmol, 1.5 equiv.) in THF (4.0 mL) was added subsequently methyl prop-2-ynal (**27**) (100 mg, 1.85 mmol, 1.0 equiv.) and 4-methylmorpholine (150 mg, 1.48 mmol, 0.8 equiv.) at 0 °C. The clear yellow solution was stirred for 15 min at 0 °C. An aqueous saturated solution of NH_4Cl (10 mL) was added, the mixture was extracted with diethyl ether (3 x 15 mL), combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, cyclohexane/ ethyl acetate = 1/1) gave the title compound as colorless oil (285 mg, 1.69 mmol, 92%). R_f = 0.18 (cyclohexane/ ethyl acetate = 1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.46 (d, *J* = 8.0 Hz, 1 H), 7.39 (d, *J* = 12.5 Hz, 1 H), 6.98 6.97 (m, 1 H), 6.19 – 6.18 (m, 1 H), 5.91 (dd, *J* = 12.5, 7.7 Hz, 1 H), 2.04 (t, *J* = 1.5 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 190.5, 170.1, 165.1, 140.8, 135.7, 114.6, 99.0, 10.7; HRMS: calc. for $C_8H_9O_4$ $[M+H]^+$: 169.0495, found: 169.0497; IR (cm^{-1}): 1776, 1671, 1641, 1617, 1361, 1343, 1185, 1135, 1093, 1055, 991, 945, 864, 745.

(*Z*)-2-iodo-3-[(4-methyl-5-oxo-2H-furan-2-yl)oxy]prop-2-enal (29): To a solution of **28** (260 mg, 1.31 mmol, 1.00 equiv.) obtained from above in dichloromethane (7.0 mL) was added N-

iodosuccinimide (415 mg, 1.79 mmol, 1.36 equiv.) and glacial acetic acid (135 µL, 2.37 mmol, 1.80 equiv.) subsequently at room temperature. The red suspension was stirred for 18 h until no starting material could be detected anymore by NMR-analysis. Triethylamine (366 µL, 2.63 mmol, 2.00 equiv.) was added slowly at 0 °C and the clear solution was stirred for 15 min at 0 °C. An aqueous saturated solution of NH_4Cl (25 mL) and dichloromethane (30 mL) and acetic acid (0.5 mL) was added, the mixture was extracted with dichloromethane (3 x 30 mL), combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, cyclohexane/ ethyl acetate = 1/1) gave the title compound *rac*-**29** as white solid (310 mg, 1.05 mmol, 80%). R_f = 0.29 (cyclohexane/ ethyl acetate = 1/1); mp = 117-119 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.77 (s, 1 H), 7.82 (s, 1 H), 7.08 (s, 1 H), 6.35 (s, 1 H), 2.08 (t, *J* = 1.5 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 185.2, 169.7, 165.3, 140.7, 136.3, 100.1, 87.8, 10.8; HRMS: calc. for $C_8H_8IO_4$ $[M+H]^+$: 294.9462, found: 294.9464; IR (cm^{-1}): 1782, 1669, 1616, 1358, 1210, 1170, 1149, 1093, 1055, 985, 954, 867. X-ray analysis was performed for racemic *rac*-**29**. Separation of enantiomers via chiral HPLC: SFC Daicel CHIRALPAK ® IB, CO_2 /*i*PrOH; *R*-stereoisomer (*R*)-**29**: R_t = 1.11 min; $[\alpha]_D^{20}$ = +119.1° (c = 1.00, $CHCl_3$, 20 °C), stereochemical assignment: CD-analysis; *S*-stereoisomer (*S*)-**29**: R_t = 2.05 min; $[\alpha]_D^{20}$ = −124.3° (c = 1.07, $CHCl_3$, 20 °C), stereochemical assignment via CD-analysis, see supporting information.

(*Z*)-2-iodo-3-[(4-methyl-5-oxo-2H-furan-2-yl)oxy]prop-2-enoic acid (31): To a solution of *rac*-**29** (85.0 mg, 289 µmol, 1.00 equiv.) obtained from above in acetonitril (2.9 mL) was added $CuBr_2$ (3.2 mg, 14.5 µmol, 0.05 equiv.) and *tert*-butylhydroperoxide (5.5 mol/L solution in decane, 260 µL, 1.45 mmol, 5.00 equiv.) subsequently at room temperature. The clear green solution was stirred for 24 h. An aqueous solution of $Na_2S_2O_3$ (10% (w/w), 10 mL), acetic acid (0.5 mL) and dichloromethane (10 mL) was added, the mixture was extracted with dichloromethane (3 x 10 mL), combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, cyclohexane/ ethyl acetate = 1/1 + 0.5% AcOH) gave the title compound as colorless oil (85.0

mg, 274 μmol, 95%). Performing this procedure using enantiomerically pure formyl vinyliodides (*R*)-**29** / (*S*)-**29** obtained as described above delivered the corresponding (*R*)-**31** and (*S*)-**31** in similar yields. R_f = 0.28 (cyclohexane/ ethyl acetate = 1/1 + 0.5% AcOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.06 (s, 1 H), 7.03 (s, 1 H), 6.29 (s, 1 H), 2.05 (t, *J* = 1.5 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 170.0, 168.5, 160.3, 140.8, 136.1, 100.1, 69.7, 10.8; HRMS: calc. for $C_8H_8IO_5$ $[M+H]^+$: 310.9411, found: 310.9410; IR (cm^{-1}) 3093, 1780, 1698, 1619, 1364, 1176, 1092, 1035, 949, 862, 735; $[\alpha]_D^{20}$ ((*R*)-**31**) = +51.5° (c = 1.12, $CHCl_3$, 20 °C), $[\alpha]_D^{20}$ ((*S*)-**31**) = –54.1° (c = 0.99, $CHCl_3$, 20 °C), see also supporting information.

Benzhydryl (*Z*)-2-iodo-3-[(4-methyl-5-oxo-2H-furan-2-yl)oxy]prop-2-enoate (32): To a solution of acid **31** (22.0 mg, 71.0 μmol, 1.0 equiv.) and diphenylmethanol (17.0 mg, 92.2 μmol, 1.3 equiv.) in dichloromethane (500 μL) was added a solution of DCC (17.6 mg, 85.2 μmol, 1.2 equiv.) and DMAP (0.9 mg, 7.10 μmol, 0.1 equiv.) in dichloromethane (500 μL). The mixture was stirred for 24 h. An aqueous saturated solution of NH_4Cl (7.0 mL) and dichloromethane (15 mL) was added. After separation the aqueous layer was extracted with dichloromethane (3 x 15 mL), combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, cyclohexane/ ethyl acetate = 2/1) gave benzhydryl compound **32** as yellowish oil (19.0 mg, 39.9 μmol, 56%). R_f = 0.31 (cyclohexane/ ethyl acetate = 2/1); ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 8.02 (s, 1 H), 7.41-7.30 (m, 10 H), 7.00 (s, 1 H), 6.89 (s, 1 H), 6.28 (s, 1 H), 2.00 (t, *J* = 1.5 Hz, 3 H); ^{13}C NMR (101 MHz, CD_2Cl_2) δ ppm 170.7, 162.7, 159.5, 141.6, 140.6, 136.4, 129.2, 129.0, 128.6, 127.5, 127.4, 127.0, 101.0, 79.6, 70.7, 11.5; HRMS: calc. for $C_{21}H_{18}IO_5$ $[M+H]^+$: 477.0199, found: 477.0197; IR (cm^{-1}): 1785, 1707, 1623, 1360, 1253, 1170, 1039, 990, 954, 748, 700.

***rac*-(*E*,2*E*)-2-[(4-methyl-5-oxo-2H-furan-2-yl)oxymethylene]-4-(2,6,6-trimethylcyclohexen-1-yl)but-3-enal (30, 19-oxo-carlacton, 19-oxo-CL):** To a solution of formyl vinyl iodide *rac*-**29** (70.0 mg, 238 μmol, 1.00 equiv.) and triphenylarsane (21.9 mg, 71.4 μmol, 0.30 equiv.) in dioxane (4.80 mL) was added vinylstannane **10** (262 mg, 595 μmol, 2.50 equiv.) under argon atmosphere. The solution was

degassed by bubbling argon through the solution for 10 min. Pd_2dba_3 (16.4 mg, 17.9 μmol, 0.075 equiv.) was added, the reaction vial was sealed and heated to 90 °C for 50 min. The yellow mixture was allowed to cool to rt, filtered over Celite (wash with cyclohexane/ ethyl acetate = 1/1, 20 mL). The solvent was removed *in vacuo* and the crude was purified by flash column chromatography (SiO_2, cyclohexane/ ethyl acetate = 2/1 to 1/1). The title compound *rac*-**30** (19-oxo-CL) was obtained as colorless oil (13.0 mg, 41.1 μmol, 18%). R_f = 0.43 (cyclohexane/ ethyl acetate = 1/1); ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 9.33 (d, *J* = 1.5 Hz, 1 H), 7.09 (s, 1 H), 7.07 (d, *J* = 16.9 Hz, 1 H), 7.02 - 7.01 (m, 1 H), 6.26-6.25 (m, 1 H), 6.06 (dd, *J* = 16.9, 1.5 Hz, 1 H), 2.01 (t, *J* = 1.5 Hz, 3 H), 2.00 (virt t, *J* = 6.2 Hz, 2 H), 1.70 – 1.69 (m, 3 H), 1.64 – 1.58 (m, 2 H), 1.47 – 1.44 (m, 2 H), 1.00 (s, 3 H), 0.99 (s, 3 H); ^{13}C NMR (101 MHz, CD_2Cl_2) δ ppm 191.0, 170.9, 161.2, 141.7, 138.8, 136.4, 134.4, 130.3, 123.0, 119.9, 101.2, 40.1, 34.5, 33.5, 29.2, 21.9, 19.8, 11.0; HRMS: calc. for $C_{19}H_{25}O_4$ $[M+H]^+$: 317.1747, found: 317.1750; IR (cm^{-1}): 2958, 2928, 2865, 1783, 1685, 1678, 1636, 1600, 1358, 1204, 1175, 1093, 1010, 955, 862.

***rac*-/ (*R*)-/ (*S*)- (*E*,2*E*)-2-[(4-methyl-5-oxo-2H-furan-2-yl)oxymethylene]-4-(2,6,6-trimethylcyclohexen-1-yl)but-3-enoic acid (3, carlactonic acid, CLA):** To a solution of vinyl iodide *rac*-**31** (19.1 mg, 61.7 μmol, 1.00 equiv.) and triphenylarsane (5.7 mg, 18.5 μmol, 0.30 equiv.) in dioxane (1.20 mL) was added vinylstannane **10** (136 mg, 309 μmol, 5.00 equiv.) under argon atmosphere. The solution was degassed by bubbling argon through the solution for 10 min. Pd_2dba_3 (4.2 mg, 4.63 μmol, 0.075 equiv.) was added, the reaction vial was sealed and heated to 90 °C for 50 min. The mixture was allowed to cool to rt, filtered over Celite (wash with cyclohexane/ ethyl acetate = 1/1, 15 mL). The solvent was removed *in vacuo* and the crude was purified by flash column chromatography (SiO_2, cyclohexane/ ethyl acetate = 2/1 + 1% AcOH). The title compound (CLA) was obtained as colorless oil (10.4 mg, 31.3 μmol, 51%). Performing this procedure using enantiomerically pure vinyliodides (*R*)-**31** / (*S*)-**31** obtained as described above delivered (*R*)-**3** and (*S*)-**3** in similar yields. R_f = 0.24 (cyclohexane/ ethyl acetate = 2/1 + 1% AcOH); ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 7.66 (s, 1 H), 6.99 - 6.97 (m, 1 H), 6.81 (d, *J* = 16.5 Hz, 1 H), 6.20 – 6.18 (m, 1 H), 6.08 (d, *J* = 16.5 Hz, 1 H), 2.00

(virt. t, J = 6.2 Hz, 2 H), 1.99 (t, J = 1.5 Hz, 3 H), 1.70 (s, 3 H), 1.63 – 1.57 (m, 2 H), 1.47 – 1.44 (m, 2 H), 1.00 (s, 6 H); ^{13}C NMR (101 MHz, CD_2Cl_2) δ ppm 172.5, 171.0, 153.6, 141.8, 138.8, 136.1, 133.5, 129.8, 122.0, 112.5, 101.3, 40.1, 34.6, 33.4, 29.1, 21.9, 19.8, 11.0; HRMS: calc. for $C_{19}H_{25}O_5$ $[M+H]^+$: 333.1697, found: 333.1696; IR (cm^{-1}): 3083, 2957, 2925, 2858, 1787, 1686, 1357, 1194, 1009, 955; $[\alpha]_D^{20}$ ((*R*)-CLA, (*R*)-**3**) = +63.4° (c = 0.30, CH_2Cl_2, 20 °C), $[\alpha]_D^{20}$ ((*S*)-CLA, (*S*)-**3**) = –62.5° (c = 0.69, CH_2Cl_2, 20 °C); see also chiral HPLC-spectra within the supporting information.

ASSOCIATED CONTENT.

Spectral data and copies of NMR spectra for all new compounds. Circular dichroism studies for (*R*)-**9**, (*S*)-**9** and (*R*)-**29**, (*S*)-**29** are included. Data for germination assay on *Orobanche Cumana*. This material is available free of charge via the Internet at http://pubs.acs.org.

X-ray data for compounds *rac*-**9** and *rac*-**29** are available on Cambridge Crystallographic Data Centre CCDC 1573373 (*rac*-**9**) and CCDC 1573432 (*rac*-**29**).

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NOTES.

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