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Enantioselective total synthesis of the phytotoxic lactone herbarumin I

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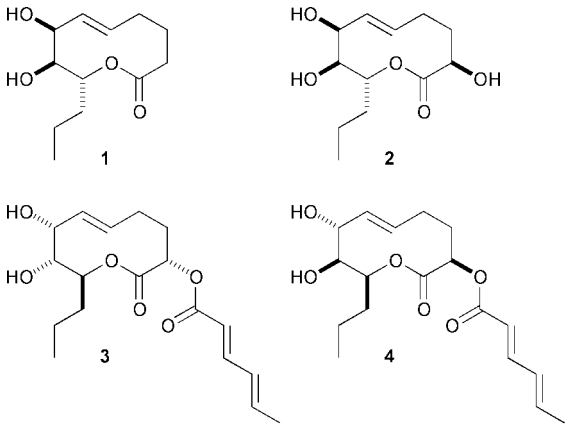
A concise total synthesis of the potent herbicide herbarumin I (1) is presented based on an (*E*)-selective RCM reaction forging the 10-membered ring of this macrolide.

Bioassay guided fractionation of a culture broth of the fungus *Phoma herbarum* recently led to the discovery of two novel nonenolides. Named herbarumin I (**1**) and herbarumin II (**2**), these lactones were found to exhibit significant phytotoxic

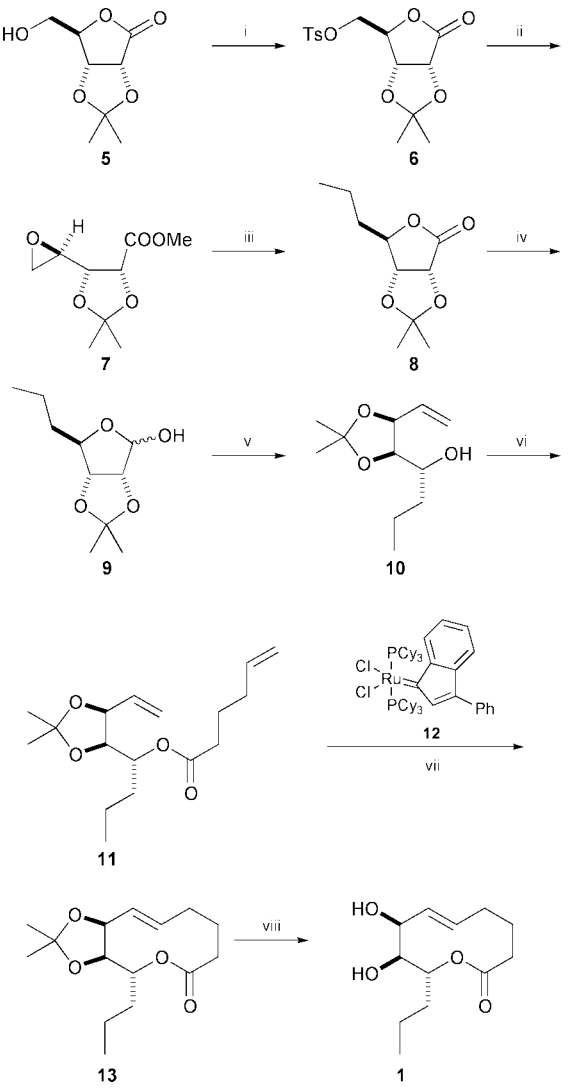


effects in an assay monitoring the radicle elongation of *Amaranthus hypochondriacus* seedlings, with IC_{50} values being as low as 5.43×10^{-5} for compound **1**.[1] This level of activity together with the fact that closely related compounds such as pinolidoxin (**3**)[2] and lethaloxin (**4**)[3] also exert significant phytotoxicity renders this class of compounds promising new lead structures in the search for novel herbicidal agents. Described below is the first total synthesis of a member of this family of natural products.

Our approach to herbarumin I (**1**) as the most active compound of this series is guided by the perception that the stereochemistry of its three contiguous chiral centers is matched by the pattern displayed by D-ribose. Therefore, the D-ribonolactone acetonide derivative **5** was chosen as a well accessible starting material which is converted on a multigram scale into tosylate **6** (Scheme 1).[4] Subsequent treatment with NaOMe in THF leads to product **7** *via* transesterification followed by spontaneous closure of the epoxide ring once the alkoxide at O-4 is liberated.[5] This compound is then exposed to the cuprate reagent formed from EtMgBr and CuBr·Me_2S in THF,[6] thus providing lactone **8** in 60% yield.† DIBAL-H reduction followed by reaction of the resulting lactol **9** with methylenetriphenylphosphorane in the presence of catalytic amounts of quinuclidine[7] delivers alcohol **10** in good yield, which is esterified with hex-5-enoic acid in the presence of DCC and DMAP to afford diene **11**. This sets the stage for the crucial macrocyclization reaction *via* ring closing olefin metathesis (RCM).

During the last decade, olefin metathesis has evolved into a versatile and practical tool for advanced organic chemistry.[8] Despite the impressive number of applications of this reaction to the synthesis of structurally diverse carbo- and heterocycles, it must be kept in mind that the formation of medium sized rings by this method still poses considerable challenges.[9,10] Because of the inherent ring strain, eight- to eleven-membered cycloalkenes are particularly prone to the reverse process, *i.e.* to ring opening metathesis (ROM) or ring opening metathesis polymerization (ROMP).

It has been shown, however, that this problem can be circumvented in many cases by incorporating suitable conformational control elements forcing the substrate to adopt a suitable conformation for ring closure. This facilitates RCM and stabilizes the product formed against the competing ROMP



Scheme 1 *Reagents and conditions*: i, tosyl chloride, pyridine, −20 °C, 16 h, 77%; ii, NaOMe, THF, 0 °C → rt, 16 h, 62%; iii, EtMgBr (3 eq.), CuBr·Me_2S (3 eq.), THF, −78 °C → rt, 16 h, 60%; iv, DIBAL-H, CH_2Cl_2, −78 °C, 2 h, 97%; v, $Ph_3P{=}CH_2$ (2 eq.), quinuclidine (0.2 eq.), THF, reflux, 30 min, 77%; vi, hex-5-enoic acid, DCC, DMAP, CH_2Cl_2, rt, 4 d, 84%; vii, catalyst **12** (10 mol%), CH_2Cl_2, reflux, 7 h, 69%; viii, aq. HCl (1 M), THF, 50 °C, 16 h, 90%.

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pathway. The isopropylidene acetal of compound **11** may act as such a temporary constraint which adequately shapes this particular diene and simultaneously confers bias upon the stereochemistry of the newly formed double bond.[11]

We were pleased to find that this is indeed the case. Treatment of compound **11** with catalytic amounts of the ruthenium indenylidene complex **12**[12] in refluxing CH_2Cl_2 affords the desired ten-membered lactone **13** as the only product in 69% isolated yield. Although applications of RCM to the synthesis of medium-sized and macrocyclic cycloalkenes are frequently plagued by the formation of *E*/*Z*-mixtures,[8,13] compound **13** was obtained as a single diastereoisomer which was assigned the *E*-configuration based on detailed NMR investigations.‡ This particular example also nicely features the excellent application profile of the ruthenium complex **12** which is equipotent or even superior to the more popular Grubbs carbene $(Cy_3P)_2(Cl)_2Ru{=}CHPh$[14] yet easier to make from stable and commercially available precursors.[12]

Final cleavage of the acetal group with dilute aq. HCl occurs uneventfully and provides herbarumin I **1** in 90% yield as a low melting solid. Although the $[\alpha]_D$ value of the synthetic sample deviates from the reported one to some extent,§ there is no doubt as to the constitution and configuration of this compound since the high resolution NMR spectra (Bruker DMX 600) as well as the IR and MS data are in excellent agreement with the proposed structure and perfectly match those reported in the literature.§

In summary, a concise total synthesis of the potent phytopathogenic macrolide herbarumin I is presented. The approach using D-ribonolactone as a convenient source of chirality is based on a highly efficient and diastereoselective RCM reaction for the formation of the ten-membered ring of the target, which is delivered in enantiomerically pure form in only 8 steps starting from **5** in ~11% overall yield. Extensions of this methodology to other members of this series of herbicidal agents are underway and will be disclosed in the near future.

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Notes and references

† Competitive attack of bromide ions on epoxide **7** could not be fully supressed; small amounts of 5-bromo-2,3-isopropylidene-D-ribono-1,4-lactone thus formed are separated by flash chromatography. In this context it should also be noted that all attempts to prepare compound **8** more directly by reaction of tosylate **6** with various ethyl donors (Et_2CuLi or EtMgBr + $CuBr{\cdot}Me_2S$) turned out to be low yielding and could not compete with the route depicted in Scheme 1.

‡ NMR investigations at this stage are hampered by the fact that compound **13** exists in two slowly interconverting conformers in solution. The assignment of the stereochemistry of the double bond, however, is unambiguous and is ultimately corroborated by the successful completion of the synthesis, providing synthetic **1** which exhibits a coupling constant of ^3J = 15.8 Hz for the vicinal olefinic protons. Details on the structural assignment of **13** will be reported in a forthcoming full paper.

§ Synthetic **1**: $[\alpha]_D^{20}$ +10.8° (*c* 0.51, EtOH); ref. **1**: $[\alpha]_D$ +28.0° (*c* 0.1, EtOH). Spectroscopic data of synthetic **1**: IR: 3450, 3033, 2960, 2929, 2872, 1716, 1631, 1203, 1058, 982 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 5.58 (ddd, 1H, *J* = 15.8, 1.7, 1.0 Hz, H-6), 5.49 (dddd, 1H, *J* = 15.8, 10.3, 4.0, 2.3 Hz, H-5), 4.92 (td, 1H, *J* = 9.6, 2.6 Hz, H-9), 4.40 (quint., 1H, *J* = 2.3 Hz, H-7), 3.48 (dd, 1H, *J* = 9.8, 2.3 Hz, H-8), 2.39 (br s, 1H, −OH), 2.38 (br d, 1H, *J* = 12.3 Hz, H-4a), 2.30 (ddd, 1H, *J* = 14.0, 5.8, 2.4 Hz, H-2a), 2.14 (br s, 1H, −OH), 1.98 (ddd, 1H, *J* = 14.0, 12.9, 2.0 Hz, H-2b), 1.92 (m, 1H, H-4b), 1.87 (m, 1H, H-3a), 1.86 (m, 1H, H-10a), 1.71 (m, 1H, H-3b), 1.54 (ddt, 1H, *J* = 14.4, 9.7, 4.8 Hz, H-10b), 1.35 (m, 1H, H-11a), 1.27 (m, 1H, H-11b), 0.89 (t, 3H, *J* = 7.3 Hz, −Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.3, 130.7, 124.7, 73.6, 73.3, 70.1, 34.4, 33.7, 33.3, 24.6, 17.9, 13.8; MS (EI): *m*/*z* (rel. intensity): 228 (3, $[M^+]$), 200 (5), 144 (10), 143 (40), 126 (16), 125 (100), 97 (33), 95 (12), 86 (29), 84 (11), 83 (24), 81 (12), 79 (19), 70 (19), 69 (14), 57 (52), 55 (28); MS (ESI): 251 ($[M + Na]^+$), 479 ($[2M + Na]^+$).

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