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Total synthesis of (+)-herbarumin I via intermolecular Nozaki–Hiyama–Kishi reaction

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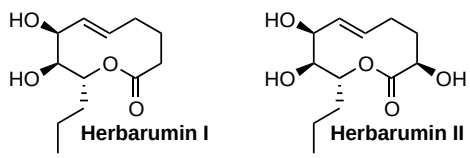
Abstract—The phytotoxin herbarumin I, isolated from *Phoma herbarum*, was stereoselectively synthesized in 17 steps and 6% yield from L-arabinose featuring the intermolecular Nozaki–Hiyama–Kishi coupling and modified Yamaguchi macrolactonization as key steps.

Recently, Mata and co-workers[1] have isolated two new phytotoxic lactones, named herbarumin I and II, from the culture of *Phoma herbarum* fungus. Related 10-membered lactones have also been isolated from fungi with phytotoxic activity such as pinolidoxin,[2] lethaloxin[3] and putaminoxin.[4]



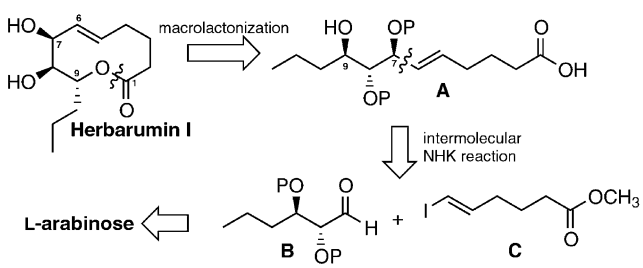
Among the substances isolated from *P. herbarum* extract, herbarumin I displayed pronounced phytotoxic activity on the seedling of *Amaranthus hypochondriacus*,[1] holding promise as a lead compound for the discovery of new herbicides. Recently, Fürstner and co-workers[5] reported the first total synthesis of herbarumin I taking advantage of an (*E*)-selective ring closing olefin metathesis (RCM) approach to prepare the lactone ring.

Our ongoing interest in the stereoselective preparation of 10-membered lactones[6] through the Nozaki–Hiyama–Kishi (NHK) reaction[7] led us to explore this approach in the total synthesis of herbarumin I. Here we disclose our results on the total synthesis of herbarumin I based on the Felkin-type intermolecular NHK reaction between α,β-alkoxy aldehyde **B** and vinylic iodide **C**, followed by macrolactonization (Scheme 1).

Starting from L-arabinose (**2**), lactol **4** was prepared in 65% overall yield according to the procedure by Ballou and Wightman.[8] Wittig olefination[9] afforded the corresponding olefin as a 3.2:1 mixture (*Z*/*E*) that was subsequently hydrogenated on Pd/C to give acetonide **6** in 85% yield for two steps.

Removal of the acid labile acetonide group and re-acetalization of the corresponding triol under thermodynamic conditions with 3-pentanone provided acetal **8** in 79% yield. This one was transformed in the corresponding benzylic ether[10] and then converted to the corresponding bis-silyl ether **11** in 78% overall yield from **8** (three steps). Selective deprotection[11] of the primary silyl group with HF·pyridine in buffered THF, followed by mild oxidation of the corresponding alcohol with Dess–Martin periodinane[12] provided aldehyde **13** in 64% yield over two steps (Scheme 2).

Hydrostannylation of 5-hexyn-1-ol (**14**) catalyzed by $Pd(PPh_3)_2Cl_2$[13] stereoselectively provided vinylic stannane **15** in 74% yield. Tin–iodine exchange was accom-



Scheme 1. Retrosynthetic analysis for herbarumin I.

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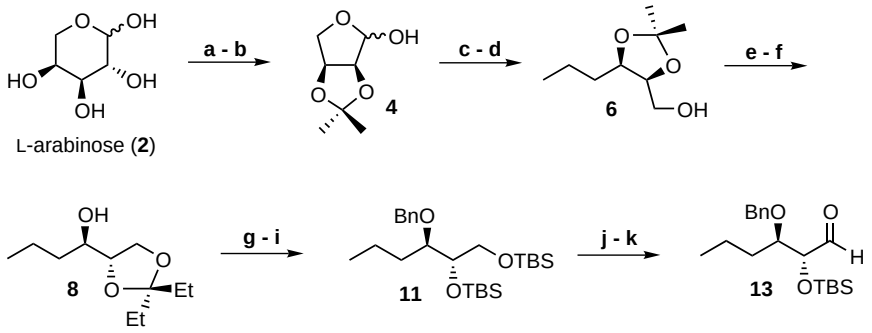
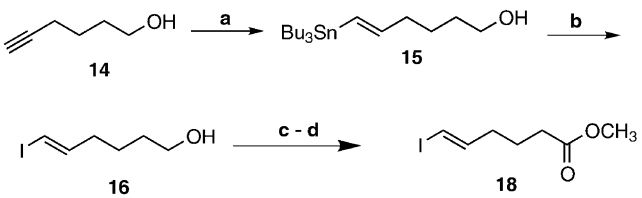


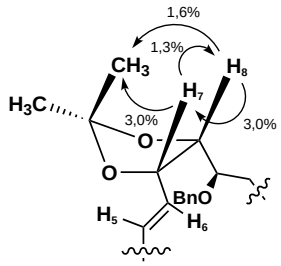
Scheme 2. *Reagents and conditions*. (a) 2,2-Dimethoxypropane, DMF, PTSA; (b) $NaBH_4$, EtOH, 2 h, then $NaIO_4$, H_2O (65% overall); (c) $C_2H_5PPh_3Br$, *n*-BuLi, THF, −78°C, 2 h, then **4** (89%); (d) H_2, Pd/C, EtOH (96%); (e) 10% HCl, MeOH, quant.; (f) 3-pentanone, CSA, rt (79%); (g) NaH, BnBr, Et_4NI, THF (82%); (h) 2 mol L^{-1} HCl, MeOH, quant.; (i) TBSCl, imidazole, DMF (95%); (j) HF.pyridine, THF, pyridine (65%); (k) Dess–Martin periodinane, CH_2Cl_2 (99%).

plished without isomerization of the double bound to afford the required vinylic iodide **16** in 93% yield. Jones oxidation followed by esterification[14] with $SOCl_2$ in methanol, afforded ester **18** in 59% yield over two steps (Scheme 3).

The intermolecular Nozaki–Hiyama–Kishi reaction of vinylic iodide **18** and aldehyde **13** was successfully carried out and provided allylic alcohol **19** together with its C7 epimer (76% yield, 3.4:1 mixture). The *anti* configuration at C7–C8 of the major isomer **19** was established after nOe experiments with its acetonide **20**: among others, a 3.0% increment at the H7 signal observed upon irradiation of H8 was diagnostic of the H7–H8 *cis* relationship.

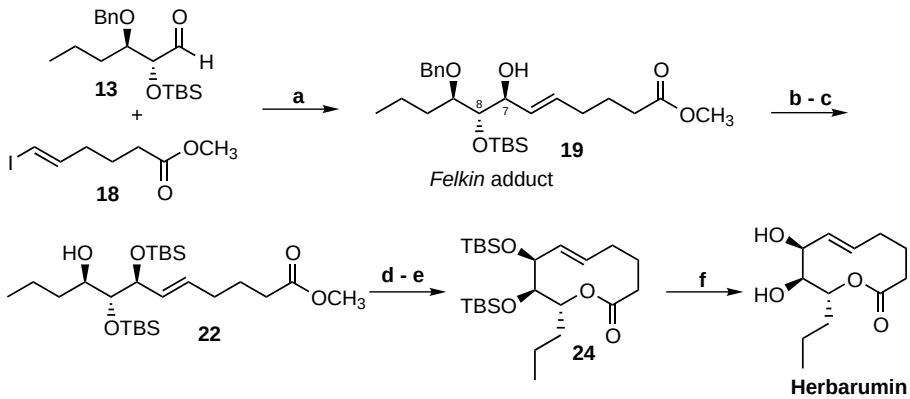


Scheme 3. *Reagents and conditions*. (a) *n*-Bu_3SnH, 2 mol% $Pd(PPh_3)_2Cl_2$, CH_2Cl_2 (74%); (b) I_2, CCl_4 (93%); (c) CrO_3, H_2SO_4, acetone (81%); (d) $SOCl_2$, MeOH, 0°C (73%).



***nOe increments in acetonide* 20**

Having secured the C7 configuration, the secondary alcohol was protected as its TBS ether and the selective removal of the benzylic group was investigated next. While no reaction was observed with lithium naphthalenide[15] or LiDBB,[16] hydrogenolysis under Raney nickel[17] promoted both the removal of the benzyl group and reduction of the double bond. Eventually, alcohol **22** was successfully prepared via hydrogen transfer reaction employing cyclohexene[18] and $Pd(OH)_2$ as catalyst, in 81% yield. Ester hydrolysis followed by lactonization under modified Yamaguchi macrolactonization[19] afforded 10-membered lactone **24** in 54% overall yield from **22**. Removal of both TBS groups with TBAF in THF as the fluoride source



Scheme 4. *Reagents and conditions*. (a) $CrCl_2$ (1% $NiCl_2$), DMSO (76%, 3.4:1 mixture); (b) TBSCl, DMF (77%); (c) $Pd(OH)_2$, EtOH/cyclohexene (2.5:1 v/v), 63°C (81%); (d) LiOH, THF/MeOH/H_2O (3:1:1 v/v) (96%); (e) 2,4,6-$Cl_3PhCOCl$, DIPEA, DMAP, benzene, 3×10^{-4} mol L^{-1}, 80°C (56%); (f) TBAF, 1.0 mol L^{-1}, THF, quant.

provided the corresponding diol in quantitative yield, which proved to be identical to herbarumin I by ^{1}H and ^{13}C NMR spectroscopy and specific optical rotation (Scheme 4).[20]

In summary, the intermolecular Nozaki–Hiyama–Kishi coupling provided the Felkin type allylic alcohol with the correct configuration for the synthesis of the potent phytotoxin herbarumin I in 17 steps (longest linear sequence) from L-arabinose and 6% overall yield. This approach is currently under investigation in our laboratory for the synthesis of other 10-membered lactones.

Acknowledgements

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20. Representative analytical data. Herbarumin I: $[\alpha]_D^{20}$ +18 (*c* 0.1; EtOH) {$[\alpha]_D^{20}$ +28 (*c* 0.1, EtOH), Ref. 1; $[\alpha]_D^{20}$ +10.8 (*c* 0.51, EtOH), Ref. 5}; IR (KBr, film): 3437, 2958, 2924, 2854, 1720, 1647, 1462, 1358, 1254, 1203, 1153, 1057 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.93 (t, 3H, $J=7.3$ Hz, Me), 1.3–1.44 (m, 3H), 1.52–1.78 (m, 3H), 1.82–2.06 (m, 3H), 2.29–2.44 (m, 3H), 3.51 (dd, 1H, $J=9.7$, 2.4 Hz, H8), 4.43 (br s, 1H, H7), 4.95 (td, 1H, $J=9.7$, 2.6 Hz, H9), 5.51 (dddd, 1H, *J* 15.8, 9.3, 3.5, 1.8 Hz, H5), 5.62 (dd, 1H, $J=16.1$, 1.5 Hz, H6); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.8, 18.0, 33.6, 70.2, 73.7, 73.3, 130.5, 124.9, 33.3, 24.7, 34.4, 176.4. Compound **19**: $[\alpha]_D^{20}$ −27.8 (*c* 1.6, $CHCl_3$); (IR (KBr, film): 3494, 3028, 2924, 2862, 1739, 1462, 1369, 1254, 1099, 841, 779, 737, 694 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.07 (s, 3H, MeSi), 0.08 (s, 3H, MeSi), 0.89 (t, 3H, $J=7.0$ Hz, Me), 0.90 (s, 9H, *tert*-Bu), 1.35 (m, 1H, H11a), 1.48 (m, 1H, H11b), 1.58 (m, 2H, H10), 1.71 (quint., 2H, $J=7.6$ Hz, H3), 2.07 (quart., 2H, $J=7.0$ Hz, H4), 2.19 (d, 1H, $J=3.7$ Hz, OH), 2.31 (t, 2H, $J=7.3$ Hz, H-2), 3.48 (dt, 1H, $J=7.6$, 4.0 Hz, H-9), 3.66 (s, 3H, –OMe), 3.76 (dd, 1H, $J=4.9$, 4.3 Hz, H8), 4.19 (br s, 1H, H7), 4.49 (d, 1H, $J=11.3$ Hz), 4.59 (d, 1H, $J=11.3$ Hz), 5.58 (dd, 1H, $J=15.5$, 6.4 Hz, H6), 5.65 (dt, 1H, $J=15.6$, 6.7 Hz, H5), 7.27–7.34 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ −4.44, −4.34, 14.18, 18.21, 18.74, 24.21, 25.93, 31.73, 32.89, 33.44, 51.48, 72.10, 74.51, 76.55, 80.86, 127.46.