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ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 7173–7176

Stereoselective synthesis of the phytotoxic nonenolide herbarumin-I from L-ascorbic acid

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Received 31 May 2007; revised 23 July 2007; accepted 30 July 2007
Available online 2 August 2007

Abstract—A stereoselective synthesis of herbarumin-I in 22% overall yield, starting from L-ascorbic acid derived (*S*)-2,3-*O*-isopropylidine glyceraldehyde as a chiral template is reported. Stereoselective allylation and vinylation to control the required stereogenic centres and macrolactonisation followed by a ring-closing metathesis (RCM) are the key steps.

Bioassay guided fractionation of a culture broth and mycelium of the fungus *Phoma herbarum* Westend (Sphaeropsidaceae) led to the discovery of three novel nonenolides named herbarumin-I (**1**), II (**2**) and III (**3**) (Fig. 1).[1] These lactones exhibited significant phytotoxic effects when tested against the seedlings of *Amaranthus hypochondriacus* at very low concentrations using a Petri dish bioassay.[2] Amongst these lactones herbarumin-I (**1**) shows promising phytotoxic effects with IC_{50} values as low as 5.43×10^{-5}. Enzyme-inhibition studies of compounds **1**–**3** also suggested an interesting behaviour superior to chlorpromazine, as calmodulin-dependent enzyme cyclic nucleotide (cAMP) phosphodiesterase calmodulin inhibitors without interfering with the basal activity or the independent form of the enzyme.[1a,3] As a result of these activities together with the fact that closely related compounds such as pinolidoxin (**4**)[4] and lethaloxin (**5**)[5] (Fig. 1) also exert significant phytotoxicity, makes this class of compounds promising new lead structures in the search for novel herbicidal agents.

Several approaches towards the asymmetric synthesis of these ten-membered lactones **1**–**3** have appeared in the literature.[6] The asymmetric synthesis of these lactones involves ring-closing metathesis (RCM) or Nozaki–Hiyama–Kishi reactions as the key steps for the formation of the ten-membered ring starting from various sugars, such as D-ribose, L-arabinose and D-glucose as chiral-pool templates. Despite the superior biological activity of herbarumin-I (**1**) compared to herbarumin-II (**2**) and herbarumin-III (**3**), only two asymmetric syntheses of **1** have been reported in the literature.[6a,b,d]

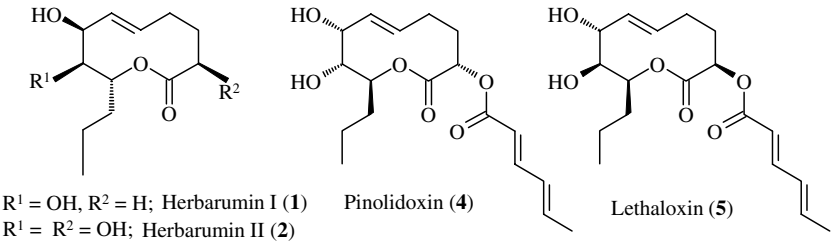

Figure 1.

Keywords: L-Ascorbic acid; Allylation; Vinylation; Macrolactonisation; Ring-closing metathesis.
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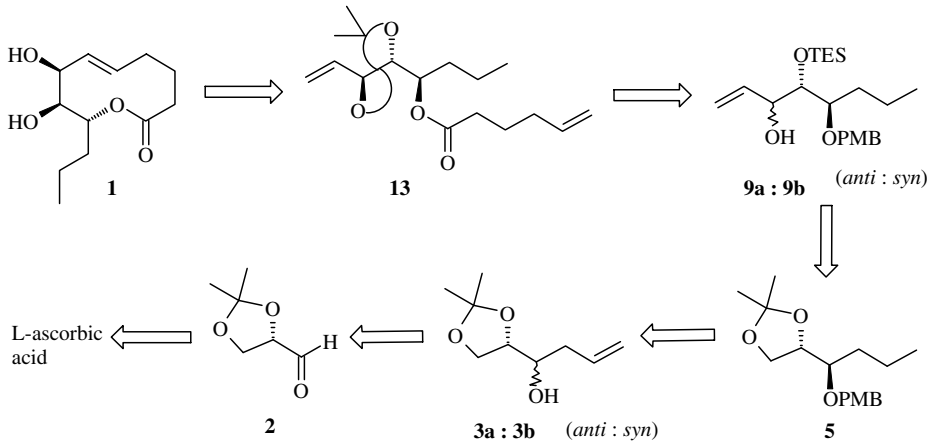
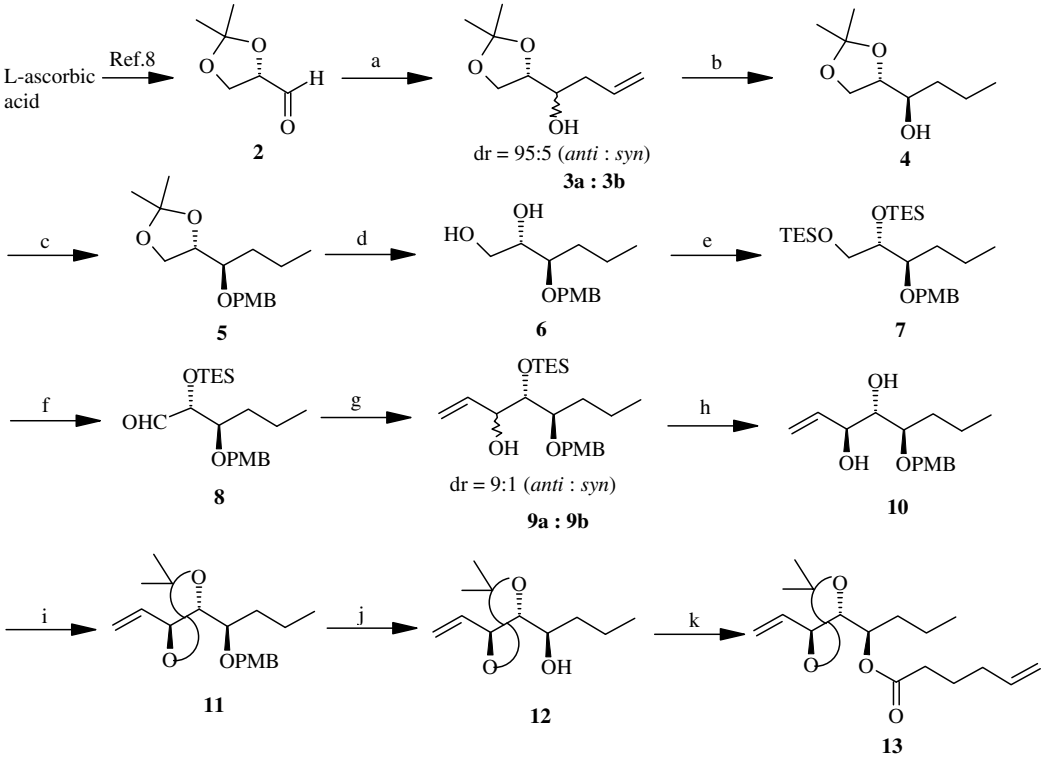
0040-4039/$ - see front matter © 2007 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2007.07.191



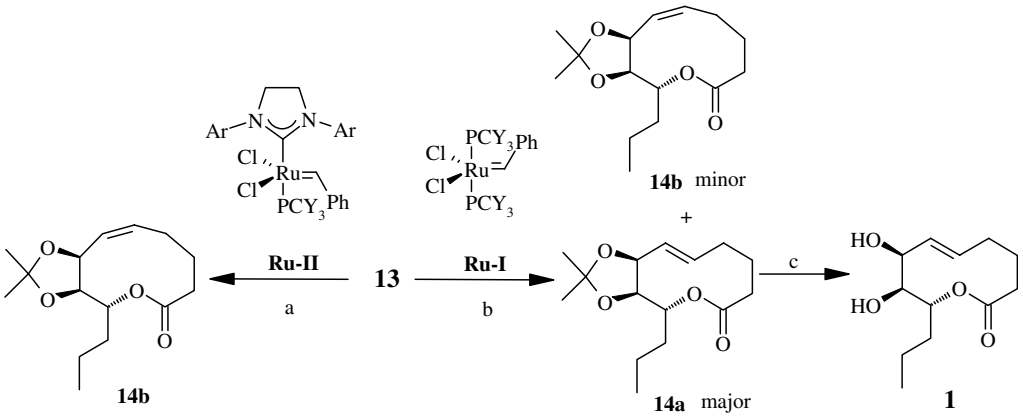
Scheme 1. Retrosynthesis of herbarumin-I (**1**).

Herein, we describe the stereoselective synthesis of herbarumin-I (**1**) starting from L-ascorbic acid derived (*S*)-2,3-*O*-isopropylidine glyceraldehyde as a chiral template. Enantioselective allylation and vinylation reactions to control the required stereogenic centres and macrolactonisation followed by a ring-closing metathesis (RCM) are key-steps. A retrosynthetic strategy for **1** is outlined in Scheme 1.

Initially we investigated the Zn-mediated[7] stereoselective allylation of (*S*)-2,3-*O*-isopropylidine glyceraldehyde **2**[8] to furnish the corresponding homoallylic alcohols **3a** and **3b** as a mixture of diastereomers (*anti*:*syn* = 95:5) in 92% overall yield which was separated by silica gel chromatography. The major diastereomer **3a** had the required stereochemistry at C-3. Homoallylic alcohol **3a** on hydrogenation using 10% Pd/C and subsequent PMB protection of the hydroxy group with PMBBr and NaH at 0 °C afforded **5**. Hydrolysis of the 2,3-*O*-isopropylidene moiety of **5** with 1 N HCl in THF at ambient temperature afforded diol **6**, which on TES-protection with 2.2 equiv of TESCl and imidazole in DCM



Scheme 2. Reagents and conditions: (a) Zn, allyl bromide, THF, satd NH_4Cl, 0 °C to rt, 4 h, 92%; (b) Pd/C, H_2, EtOH, rt, 4 h, 100%; (c) PMBBr, NaH, THF, 0 °C to rt, 4 h, 85%; (d) 1 N HCl, THF, rt, 6 h, 95%; (e) TESCl, imidazole, DCM, 0 °C to rt, 3 h, 85%; (f) $(COCl)_2$, dry DMSO, Et_3N, DCM, −78 °C, 3 h, 80%; (g) vinylmagnesium bromide, dry THF, 0 °C to rt, 3 h, 90%; (h) 1 N HCl, THF, rt, 3 h, 92%; (i) 2,2-DMP, cat. PPTS, rt, 6 h, 95%; (j) DDQ, DCM–H_2O (19:1), rt, 1 h, 92%; (k) 5-hexenoic acid, 2,4,6-trichlorobenzoyl chloride, DMAP, THF, **12** in THF, 0 °C to rt, 4 h, 85%.



Scheme 3. Reagents and conditions: (a) 30 mol % **Ru-II**, CH_2Cl_2, reflux, 12 h, (85% *Z*-isomer); (b) 30 mol % **Ru-I**, CH_2Cl_2, reflux, 8 h, (*E*:*Z* = 80:20 = 82%); (c) 1 N HCl, THF, 50 °C, 4 h, 87%.

provided di-TES compound **7**. Compound **7** on Swern oxidation[9] furnished aldehyde **8** via domino deprotection of the primary *O*-TES group and subsequent oxidation of the primary alcohol in 80% yield. Stereoselective vinylation of aldehyde **8** with in situ generated vinylmagnesium bromide afforded the corresponding allylic alcohols as a mixture of diastereomers **9a** and **9b** (*anti*:*syn* = 90:10) in 90% overall yield and these diastereomers were separated by silica gel chromatography. The major diastereomer **9a** had the required stereochemistry at C-3. Compound **9a** on treatment with 1 N HCl gave diol **10**, which on reaction with 2,2-DMP in the presence of PPTS furnished acetonide **11**. PMB deprotection of **11** with DDQ yielded intermediate **12**, whose spectral and optical rotation values were in good agreement with the literature.[6a,b] Esterification of the hydroxyl group of **12** with 5-hexenoic acid[10] under Yamaguchi conditions[11] at room temperature afforded **13** in 85% yield, which has all the structural requirements as well as sense of chirality for the ring-closing metathesis (Scheme 2).

The RCM of **13** in the presence of Grubbs' second-generation catalyst led to the exclusive formation of the undesired (*Z*)-isomer **14b** in 85% yield, whose spectral data compared well with that reported in the literature.[6b] However, compound **13**, in the presence of Grubbs' first generation catalyst yielded an *E*/*Z* mixture of cyclic olefins (**14a**:**14b** = *E*:*Z* = 80:20) in 82% overall yield.[12] The diastereomers were separated by chromatography using an $AgNO_3$–silica gel column. Cleavage of the acetal group in diastereomer **14a** under acidic conditions afforded herbarumin-I (**1**),[13] whose spectral and analytical data were consistent with those reported in the literature (Scheme 3).[1,6b]

In summary, we have developed a simple, convenient and efficient approach for the synthesis of herbarumin-I involving a sequence of reactions starting from (*S*)-2,3-*O*-isopropylidene glyceraldehyde. This approach offers a high overall yield, useful stereoselectivity and readily available starting materials at low cost and involves simple experimental conditions, which makes it a useful and attractive process for the total synthesis of herbarumin-I.

Acknowledgement

D.S. and R.S.R. thank CSIR, New Delhi, for the award of fellowships.

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13. *Spectral data for selected products*: *1-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-but-3-en-1-ol* (**3a**): Pale yellow oil; $[\alpha]_D^{25}$ −5.40 (*c* 0.5, MeOH); IR (neat): ν_{max}: 3454 (br, OH), 2986, 1375, 1214, 1064 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$); δ 5.90–5.70 (m, 1H), 5.20–5.00 (m, 2H), 4.00–3.90 (m, 3H), 3.75–3.65 (m, 1H), 2.40–2.20 (m, 2H), 1.40–1.30 (d, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): 134.0, 118.0, 109.0, 88.0, 71.0, 65.2, 37.5, 27.8, 25.2; MS-EIMS: *m/z* (%): 172 (M^+, 5), 157 (10), 141 (13), 101 (70), 59 (35), 43 (100); HRMS calcd for $C_9H_{16}O_3Na$, 195.0997; found, 195.0990; *5-(4-methoxy-benzyloxy)-4-triethylsilanyloxy-non-1-en-3-ol* (**9a**): Pale yellow oil; $[\alpha]_D^{25}$ +18.0 (*c* 1.0, $CHCl_3$); IR (neat): ν_{max}: 3292, 2956, 2871, 1612, 1515, 1251, 1086, 1036 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.20 (d, $J = 8.3$ Hz, 2H), 6.80 (d, $J = 9.0$ Hz, 2H), 6.00–5.90 (m, 1H), 5.30 (dt, $J = 17.3$, 1.5 Hz, 1H), 5.18 (dt, $J = 10.5$, 1.5 Hz, 1H), 4.45 (dd, $J = 17.3$, 10.5 Hz, 2H), 4.24 (t, $J = 6.0$ Hz, 1H), 3.80 (s, 3H), 3.74 (t, $J = 5.2$ Hz, 1H), 3.50–3.42 (m, 1H), 2.20–2.18 (br s, OH, 1H), 1.60–1.30 (m, 4H) 1.00–0.80 (m, 12H), 0.70–0.50 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.7, 142.3, 130.0, 128.7, 128.2, 127.5, 126.2, 122.5, 119.0, 114.8, 75.8, 66.6, 57.4, 45.7, 24.4; MS-ESIMS: *m/z* 417 $(M+Na)^+$; HRMS calcd for $C_{22}H_{38}O_4NaSi$, 417.2437; found, 417.2447; *1-(2,2-Dimethyl-5-vinyl-[1,3]dioxolan-4-yl)-butan-1-ol* (**12**): Pale yellow oil; $[\alpha]_D^{25}$ +7.50 (*c* 1.2, CH_2Cl_2); IR (neat): ν_{max}: 3460, 2930, 1642, 1372, 1252, 1062 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 6.00 (ddd, $J = 17.0$, 10.2, 7.2 Hz, 1H), 5.34 (dd, $J = 17.0$, 10.2 Hz, 2H), 4.58 (t, $J = 7.2$ Hz, 1H), 3.90 (t, $J = 7.2$ Hz, 1H), 3.65–3.55 (m, 1H) 1.65–1.55 (m, 2H), 1.50–1.30 (m, 8H), 0.95 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 135.0, 119.0, 108.5, 80.5, 79.0, 69.5, 35.9, 28.9, 25.3, 18.9,14.0; LC–MS: *m/z* (%): 223 ($M+Na^+$, 10), 200 (M^+, 5). *Herbarumin-I* (**1**): colourless solid; $[\alpha]_D^{25}$ +12.0 (*c* 0.5, EtOH); IR (KBr): ν_{max}: 3431, 2925, 2854, 1630, 1460, 1203, 1090 cm^{-1};^1H NMR (300 MHz, $CDCl_3$): δ 5.57 (d, $J = 15.6$ Hz, 1H), 5.50 (m, 1H), 4.87 (td, $J = 9.4$, 2.4 Hz, 1H), 4.35 (br s, 1H), 3.41 (d, $J = 9.4$ Hz, 1H), 2.43 (br s, OH, 1H), 2.22–2.33 (m, 2H), 2.07–1.80 (m, 3H), 1.48–1.70 (m, 3H), 1.30–1.20 (m, 3H), 0.92 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 176.0, 130.6, 124.9, 73.7, 73.4, 70.2, 34.4, 33.7, 33.4, 24.7, 18.0, 13.8; MS-LCMS: *m/z* 251 $(M+Na)^+$; HRMS calcd for $C_{12}H_{20}O_4Na$, 251.1259; found, 251.1269.