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Stereoselective total synthesis and cytotoxic evaluation of C-9 epimers of herbarumin-II and its C-2 epimer ☆

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ABSTRACT

The total synthesis and cytotoxic evaluation of C-9 epimers of herbarumin-II and its C-2 epimer are described for the first time. The key transformations of the synthesis include Wittig olefination, MacMillan α-hydroxylation, Pinnick oxidation, Yamaguchi esterification, and intramolecular ring closing metathesis.

Nonenolides (10-membered macrolides), an important class of natural products with interesting structural features, have been found to exhibit important biological properties such as anticancer, antifungal, antibacterial and antiviral activities.[1] They have attracted much attention to chemists and biologists in recent years.[2] Herbarumin-II (**1**), a phytotoxic nonenolide was isolated in 2000 from the fungus *Phoma herbarum* (Sphaeropsidaceae).[3] The compound contains three hydroxyl groups (all are of β-configuration) at C-2, C-7, and C-8 positions, a *trans*-substituted double bond and an appended a *n*-propyl unit at C-9 position. The lactone showed a high phytotoxic effect on seedling growth. In 2007, herbarumin-II (**1**) and its C-2 epimer (**2**) were isolated along with a hexaketide from the leaf lesions of Pendulous Yucca (*Yucca recurvifolia*).[4] The nonenolide (**2**) contains the hydroxyl group at C-2 position with α-configuration.

The synthesis of both the compounds **1** and **2** has been accomplished.[5] However, the present work is the first report of the synthesis of their C-9 epimers (**1a** and **2a**) (Fig. 1). Compounds **1a** and **2a** bear a *n*-propyl unit with β-configuration at C-9 position.

In continuation of our work[6] on the construction of naturally occurring bioactive molecules we have realized that compounds **1a** and **2a** can be synthesized from the dienes **3** and **3a**, respectively (Scheme 1). The required dienes **3** and **3a** can be obtained from the alcohol fragment **4** and the acid fragments **5** (for **3**) and **5a** (for **3a**). The alcohol **4** can in turn, be prepared from D (−) ribose and acids **5** and **5a** from hex-5-ene-1-ol.

The present synthesis was initiated by protecting D (−) ribose on treatment with acetone in the presence of concentrated H_2SO_4 (cat.) to give the lactol **6**[7] which by reacting with Ph_3PCH_3Br and K^tOBu, gave the diol **7** (Scheme 2).[8] Selective TBS protection of the primary alcohol in diol **7** with TBS-Cl produced the TBS ether **8**. The free secondary hydroxyl group in **8** was mesylated with MsCl in the presence of *N*-methyl imidazole followed by TBS deprotection with TBAF and subsequent DBU treatment to afford the epoxide **9**.[9] The epoxide ring of **9** was then opened with Mg and EtBr using CuI to afford the desired alcohol **4**.

Synthesis of the required acid fragments **5** and **5a** was started from hex-5-en-1-ol. The hex-5-en-1-ol was oxidized with SO_3Py[10] in CH_2Cl_2/DMSO (3:1) to afford the corresponding aldehyde. Subsequently, MacMillan α-aminoxylation[11] of the generated aldehyde with nitrosobenzene in the presence of D-proline, followed by treatment with $NaBH_4$ in MeOH gave the crude aminooxy alcohol. Treatment of aminooxy alcohol with (30 mol %) $CuSO_45H_2O$ afforded the chiral diol **10** in 70% overall yield (ee 97%). The primary hydroxyl group of **10** was protected as TBS ether **11** by treatment with TBS-Cl and imidazole and the free hydroxyl group of **11** was protected as MOM ether **12** by reaction with MOM-Cl and DIPEA. Compound **12** was then treated with TBAF to furnish the corresponding primary alcohol **13**. This was

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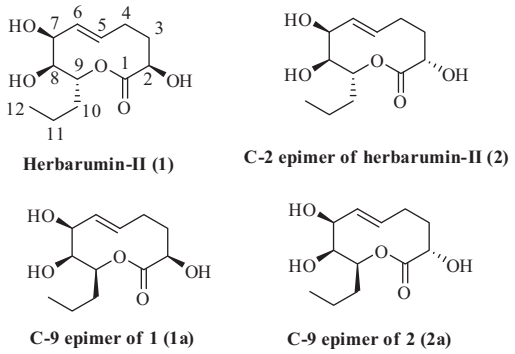
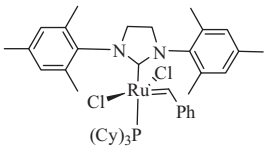


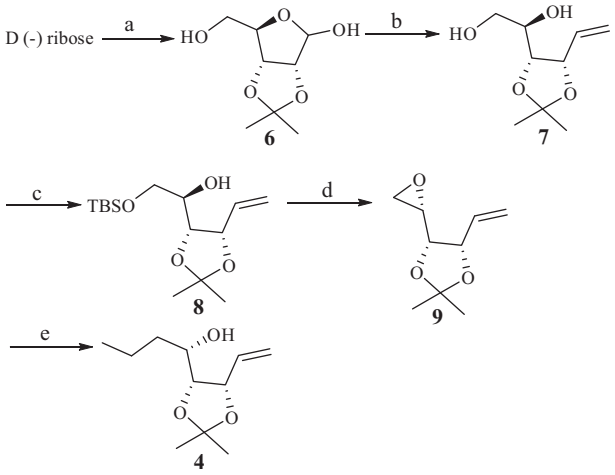
Figure 1. Structures of nonenolides.

converted into acid **5** by a two-step sequence; oxidation of **13** with DMP[12] in CH_2Cl_2 gave the corresponding aldehyde and oxidation of the aldehyde under Pinnick conditions[13] ($NaClO_2$, NaH_2PO_4, *t*-BuOH/H_2O/2-methylbut-2-ene) gave the acid **5** in 90% yield over the two steps (Scheme 3). The required enantiomeric acid fragment **5a** was synthesized starting from 5-hexene-1-ol by using MacMillan α-aminoxylation[11] with L-proline as the catalyst, by following the same sequence of the reactions as followed in the synthesis of the acid fragment (**5**).

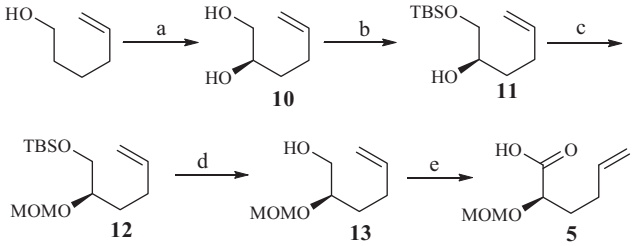
After successful achievement of required alcohol **4** and acid fragments **5** and **5a**, the alcohol fragment **4** was coupled with acid fragments **5** and **5a** individually under Yamaguchi esterification protocol[14] to afford the dienes **3** and **3a**, respectively (Scheme 4). The obtained dienes **3** and **3a** were successfully utilized to make 10-membered ring systems (macrolides) by treatment with Grubbs' second generation catalyst (**A**)[15] to yield the nonenolides **14** and **14a**. Finally, deprotection of the acetonide group in **14** and **14a** was achieved with 4 *N* HCl in CH_3CN to afford the target C-9 epimers (**1a** and **2a**) of **1** and **2**, respectively.

The spectral (^1H and ^{13}C NMR and MS) properties of the synthesized compounds **1a** and **2a** are in good agreement with their structures.[16] The structures of the compounds **1a** and **2a** were also supported by their 2D-NMR spectra. The NOESY data clearly showed the correlation between H-8 (δ 4.58 (1H, m) for **1a** and δ 4.40 (1H, m) for **2a**) and H-9 (δ 4.67 (1H, dd, *J* = 9.8, 4.5 Hz) for **1a** and δ 4.73 (1H, m) for **2a**) of these two compounds.





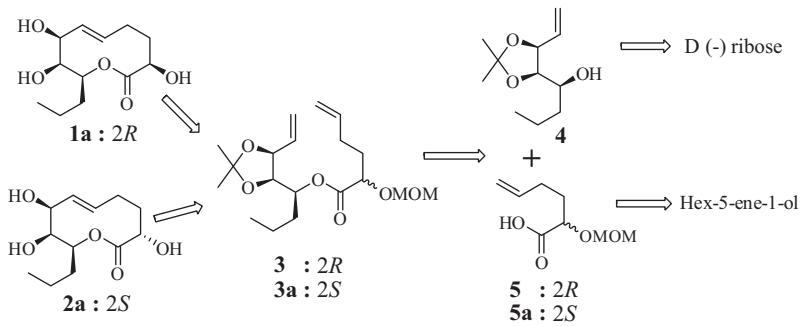
Scheme 2. Reagents and conditions: (a) acetone, con. H_2SO_4 (cat.), 6 h, rt, 96%; (b) Ph_3PCH_3Br, NaHMDS, THF, N_2, 0 °C–rt, 10 h, 86%; (c) TBS-Cl, imidazole, THF, 0 °C–rt, 2 h, 98%; (d) (i) MsCl, Et_3N, *N*-methyl imidazole, 12 h, (ii) TBAF, THF, 0 °C–rt and then (iii) DBU, CH_2Cl_2, 40 °C, 28 h, 96% (for three steps); (e) EtMgBr, CuI, −50 °C to rt, 94%.



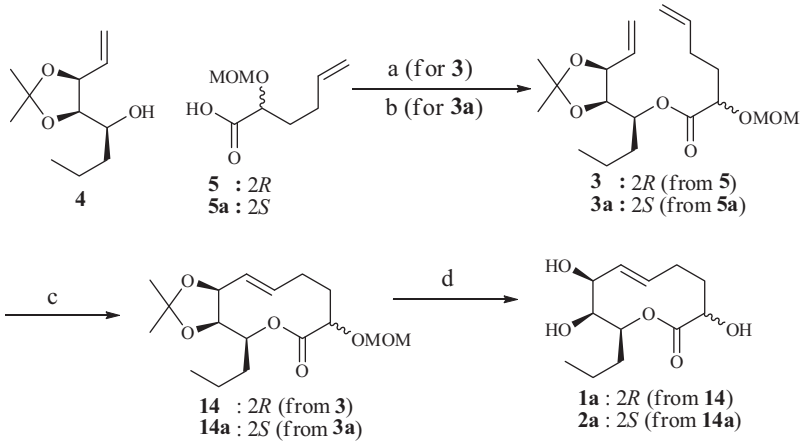
Scheme 3. Reagents and conditions:(a) (i) SO_3Py, CH_2Cl_2/DMSO (3:1), 0 °C, 1 h and then (ii) D-proline, PhNO, DMSO, 0 °C–rt, 1 h, $NaBH_4$, MeOH, then (30 mol %) $CuSO_45H_2O$ (70% for three steps); (b) TBS-Cl, imidazole, THF, 0 °C–rt, 1 h, 96%; (c) MOM-Cl, CH_2Cl_2, DIPEA, 0 °C–rt, 3 h, 98%; (d) TBAF, THF, 0 °C–rt, 2 h, 94%; (e) (i) DMP, CH_2Cl_2, 0 °C, 1 h then $NaClO_2$, NaH_2PO_4, *t*-BuOH/H_2O/2-methylbut-2-ene, 0 °C, 2 h (90% for two steps).

Cytotoxic activity

The two compounds, C-9 epimers (**1a** and **2a**) were examined for in vitro cytotoxicity against a panel of four human cancer cell lines: Neuro-2a (Mouse neuro blastoma cell line), HeLa (Human cervical cancer cell line), DU145 (Human prostate cancer cell line), and SKOV3 (Human ovarian cancer cell line). Doxorubicin was used as the positive control. MTT assay (according to the method of Mosmann[17]) was applied to assess the cytotoxic activity of the two compounds. IC_{50} values (in μM) are indicated as means ± SD



Scheme 1. Retrosynthesis of C-9 epimers **1a** and **2a**.



Scheme 4. Reagents and conditions: (a) **5**, 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, THF, rt, 94%; (b) **5a**, 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, THF, rt, 90%; (c) Grubbs' 2nd generation catalyst, CH_2Cl_2, 50 °C, 83%; (d) 4*N* HCl, CH_3CN, 0 °C–rt, 8 h, 90%.

Table 1
Cytotoxicity of C-9 epimers (**1a** and **2a**) against human cancer cell lines

Cell line	IC_{50} values in μM		
	Compound (**1a**)	Compound (**2a**)	Doxorubicin (control)
Neuro-2a	>100	16.0 ± 0.42	0.6 ± 0.08
HeLa	>100	12.3 ± 0.22	0.8 ± 0.09
DU145	>100	15.8 ± 0.28	0.9 ± 0.08
SKOV3	>100	11.6 ± 0.32	0.7 ± 0.09

of three independent experiments depicted in Table 1. The results showed that only compound **2a** exhibited moderate cytotoxic activity against all four cancer cell lines. The values observed were >100 μM for all the tested cell lines in case of compound **1a**.

In conclusion, we have developed the stereoselective total synthesis of the C-9 epimers of herbarumin-II and its C-2 epimer. The synthesis utilized D (−) ribose and hex-5-ene-1-ol as starting materials and MacMillan α-hydroxylation, Pinnick oxidation, Yamaguchi esterification, and intramolecular ring closing metathesis as the key steps. This is the first report of the synthesis of C-9 epimers of herbarumin-II and its C-2 epimer. The cytotoxic activity of the synthetic compounds **1a** and **2a** has been evaluated.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.06.011.

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16. *Spectral data of compounds **1a** and **2a**:*
Compound **1a**: IR (KBr): 3523, 3391, 2924, 2863, 1731, 1457, 1211, 1088, 937, 765 cm^1; $[\alpha]_D^{27}$: −4.3 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 5.58 (1H, dd, *J* = 16.0, 4.0 Hz), 5.49 (1H, ddd, *J* = 16.0, 9.0, 2.0 Hz), 4.67 (1H, dd, *J* = 9.8, 4.5 Hz), 4.58 (1H, m), 4.05–3.95 (2H, m), 2.41 (1H, q, *J* = 11.3 Hz), 2.27 (1H, m), 2.17 (1H, m), 1.83 (1H, m), 1.65 (1H, m), 1.41 (1H, m), 1.32–1.21 (2H, m), 0.93 (3H, t, *J* = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.2, 133.4, 126.6, 76.3, 73.3, 71.0, 66.8, 35.4, 29.7, 22.8, 17.8, 14.1; MS (ESI) (*m*/*z*): 245 $[M+H]^+$; Anal Calcd. for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25%. Found: C, 58.91; H, 8.28%; Compound **2a**: IR (KBr): 3413, 2926, 2862, 1705, 1278, 1061, 988, 770 cm^1; $[\alpha]_D^{27}$: +5.4 (*c* 1.0, MeOH); ^1H NMR (500 MHz, $CDCl_3$+DMSO-d_6): δ = 5.61–5.48 (2H, m), 4.73 (1H, m), 4.68 (1H, m), 4.40 (1H, m), 3.94 (1H, m), 3.88 (1H, br s), 3.71 (1H, br s), 3.48 (1H, br s), 2.81 (1H, q, *J* = 11.9 Hz), 2.03 (1H, m), 1.98–1.83 (2H, m), 1.65 (1H, m), 1.40 (1H, m), 1.31–1.23 (2H, m), 0.92 (3H, t, *J* = 7.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$+DMSO-d_6): δ = 172.2, 133.2, 127.0, 75.1, 73.9, 69.8, 66.1, 35.3, 33.8, 20.5, 18.0, 13.8; MS (ESI) (*m*/*z*): 445 $[M+H]^+$; Anal Calcd. for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25%. Found: C, 58.94; H, 8.32%.
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