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Total synthesis of antifungal gamahonolide A

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ABSTRACT

The first stereoselective total synthesis of gamahonolide A (**1**) has been accomplished using aminoxylation, Keck allylation, and ring-closing metathesis (RCM) reactions as key steps.

6-Substituted α,β-unsaturated δ-lactone moiety containing natural products attracted the attention of synthetic chemists due to their interesting structure and potential biological activities. The activities include antiviral, antifungal, antibacterial, growth inhibitory, antitumor, and antileukemic.[1,2] Gamahonolide A[3] (**1**) is a δ-lactone, isolated from stromata of phytopathogenic fungus, *Epichloe typhina* on *Phleum pratense*. *E. typhina* causes choke disease to the pasture grass, timothy, *P. pratense*. Gamahonolide structure was determined by spectroscopic methods and the absolute configuration by its ORD spectrum and ^{1}H NMR shift difference between the diastereomeric pair of its *O*-methylmandelates. To the best of our knowledge, the synthesis of gamahonolide A (**1**) has not been reported to date. In continuation of our program on the total synthesis of bioactive α,β-unsaturated δ-lactone containing natural products,[4] herein we report the first total synthesis of gamahonolide A (**1**) (Fig. 1) by a simple synthetic strategy.

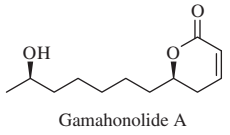
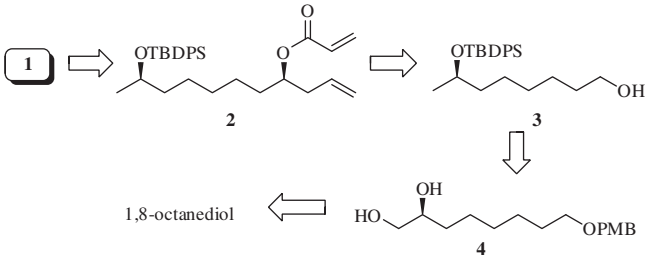


Figure 1. Structure of Gamahonolide A.

Retrosynthetic analysis of **1** is outlined in Scheme 1. Ring-closing metathesis reaction and removal of the functional group in compound **2** would provide the target molecule, whereas, RCM precursor **2** could be made available from **3** by oxidation followed by Keck allylation and acryloylation. This in turn could be made from octane-1,8-diol via compound **4** by adopting α-aminoxylation reaction as a key step.



Scheme 1. Retrosynthetic analysis.

To begin the synthesis, octane-1,8-diol was selectively monoprotected as its PMB ether **5** and the remaining hydroxyl group was oxidized to the corresponding aldehyde. The aldehyde without isolation was subjected to the MacMillan α-hydroxylation[5] using nitroso benzene and 40 mol % of D-proline in $CHCl_3$, followed by rapid reduction with sodium borohydride to furnish the unstable anilinoxy compound which was further treated with Zn in acetic acid at room temperature to cleave the O—N bond providing the diol **4** with high enantioselectivity (98.6% ee)[6] (Scheme 2). This resulting 1,2-diol **4** on treatment with TsCl, and Et_3N in the presence of dibutyltin oxide was monosilylated which on further reduction with LAH in THF provided terminal methyl compound

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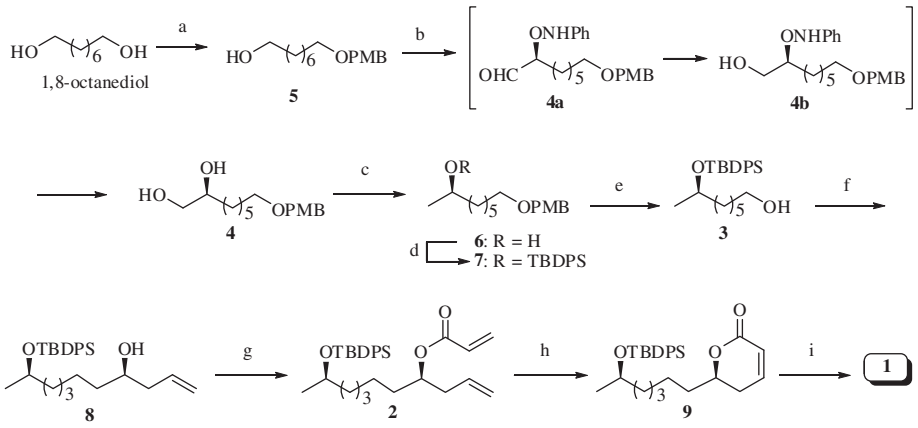

Scheme 2. Reagents and conditions: (a) NaH, PMB-Br THF, 0 °C–rt, 80%; (b) (i) IBX, DMSO, CH_2Cl_2, 3 h; (ii) PhNO, D-proline, $CHCl_3$, 0 °C, 2 h then $NaBH_4$, EtOH, 0 °C, 2 h then AcOH, Zn, rt, 12 h, 55% for 3 steps; (c) (i) TsCl, Et_3N, dibutyltin oxide (cat), dry CH_2Cl_2, 0 °C to rt, 12 h; (ii) $LiAlH_4$, THF, reflux, 3 h, 85% (for 2 steps); (d) TBDPSCl, imidazole, CH_2Cl_2, 0 °C, 3 h, 95%; (e) DDQ, CH_2Cl_2:H_2O (9:1), 0 °C, 2 h, 90%; (f) (i) IBX, DMSO, CH_2Cl_2, 3 h; (ii) (*S*)-BINOL, 4 Å MS, Ti(O*i*-Pr)$_4$, Allyl-tributylstannane, CH_2Cl_2, −78 °C to −20 °C, 24 h, 83% (for 2 steps); (g) acryloyl chloride, NaH, THF, 0 °C, 87%; (h) Grubbs' 2nd generation catalyst (G-II, 10 mol %), CH_2Cl_2, reflux, 1 h, 72%; (i) TBAF, THF, 0 °C–rt, 85%.

6. The secondary alcohol silylated using TBDPSCl and imidazole to silyl ether **7** followed by removal of the PMB group resulted in **3**. IBX oxidation of alcohol provided aldehyde which was allylated following Keck's protocol[7] to give homoallyl alcohol **8** with high diastereoselectivity (83%, 98% de).[8]

Acrylation of **8** was achieved by treatment with acryloyl chloride and NaH in THF to obtain diene **2** in 87% yield. Ring-closing metathesis[9] of **2** proceeded well with 10 mol % of Grubbs-II to produce lactone **9** in 72% yield. Finally, desilylation with TBAF in THF afforded the target gamahonolide A (**1**) in 85% yield. This compound is identical in all respects to the reported natural product including NMR, optical rotation.

In conclusion, we have accomplished the first total synthesis of gamahonolide A by a simple strategy involving α-aminoxylation, Keck allylation, and ring closing-metathesis as the key steps.

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Supplementary data

Supplementary data (copies of ^{1}H NMR, ^{13}C NMR spectra available) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.04.026.

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Spectral data for selected compounds:
Compound **4**: $[\alpha]^{25}_D$ +9.0 (*c* = 0.5, $CHCl_3$). IR (neat): 3243, 2933, 2855, 1613, 1514, 1249, 1033, 816. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.26 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 4.43 (s, 2H), 3.81 (s, 3H), 3.73–3.62 (m, 2H), 3.45–3.40 (m, 3H), 1.64–1.56 (m, 4H), 1.48–1.30 (m, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.7, 130.3, 128.9, 113.4, 72.1, 69.8, 66.3, 54.9, 32.7, 29.3, 29.2, 25.8, 25.6. ESI-MS: *m/z* 305 $[M+Na]^+$. HRMS (ESI): calc. 305.1723 $C_{16}H_{26}O_4Na$, found 305.1719; *Compound* **8**: $[\alpha]^{25}_D$ −0.20 (*c* = 0.1, $CHCl_3$). IR (neat): 3416, 2930, 2857, 1637, 1108, 703. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.70–7.65 (m, 4H), 7.44–7.34 (m, 6H), 5.87–5.74 (m, 1H), 5.16–5.08 (m, 2H), 3.87–3.79 (m, 1H), 3.64–3.52 (m, 1H), 2.16–2.03 (m, 2H), 1.52–1.15 (m, 10H), 1.07 (d, *J* = 6.1 Hz, 3H), 1.05 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 135.8, 134.8, 134.5, 129.4, 129.3, 127.4, 127.3, 118.0, 70.4, 69.3, 41.8, 39.2, 36.6, 26.9, 23.1, 21.2. ESI-MS: *m/z* 447 $[M+Na]^+$. HRMS (ESI): calc. 447.2689 $C_{27}H_{40}O_2NaSi$, found 447.2694 $[M+Na]^+$; *Compound* **1**: $[\alpha]^{25}_D$ −67.5 (*c* = 0.2, $CHCl_3$). IR (neat): 3449, 2925, 2855, 1713, 1649, 1256, 1093, 769. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.91 (ddd, *J* = 9.7, 5.4, 3.8 Hz, 1H), 6.02 (ddd, *J* = 10.0, 1.8, 1.5 Hz, 1H), 4.47–4.40 (m, 1H), 3.82 (ddq, *J* = 6.2, 6.1, 5.9 Hz, 1H), 2.36–2.31 (m, 2H), 1.85–1.75 (m, 1H), 1.73–1.56 (m, 2H), 1.52–1.38 (m, 7H), 1.20 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 164.4, 144.9, 121.4, 77.9, 68.0, 39.1, 34.7, 29.4, 29.3, 25.5, 24.8, 23.5. ESI-MS: *m/z* 235 $[M+Na]^+$. HRMS (ESI): calc. 235.13047 $C_{12}H_{20}O_3Na$, found 235.13106 $[M+Na]^+$.