Stereoselective Total Synthesis of psiAβ – A Sporogenic Psi Factor from *Aspergillus nidulans*[1]

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Abstract: The stereoselective total synthesis of psiAβ, a sporogenic psi factor of the fungus *Aspergillus nidulans*, has been accomplished starting from pentane-1,5-diol. The synthesis involves an enantioselective Keck allylation, an asymmetric alkynylzinc addition, and a TEMPO–bis(acetoxy)iodobenzene (BAIB) oxidation as the key steps.

Key words: psiAβ, total synthesis, Keck allylation, alkynylzinc addition, TEMPO, bis(acetoxy)iodobenzene , oxidation

The hydroxylated unsaturated fatty acid derivatives psiAα (**1**) and psiAβ (**2**) were isolated from the growth medium of the fungus *Aspergillus nidulans*, strain WIM-145 (Figure 1).[2] These compounds behave as precocious sexual inducer (psi) factors, inducing premature sexual sporulation in the fungus. They may function in a 'hormonal' role in regulating the sporulation cycle.[3]

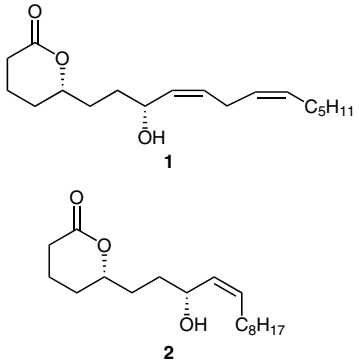
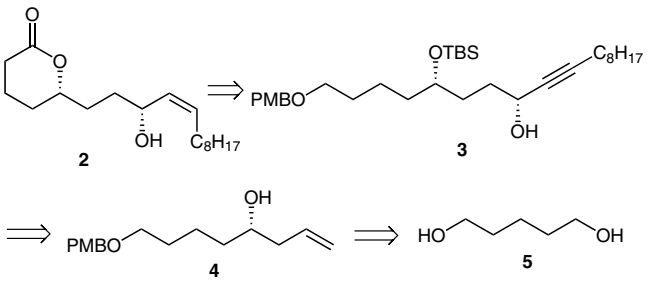


Figure 1

In continuation of our work[4] on the construction of bioactive natural molecules, we herein disclose the stereoselective total synthesis of psiAβ (**2**). A chemoenzymatic method for the synthesis of **2** has been previously reported.[5]

Retrosynthetic analysis (Scheme 1) suggested that compound **2** could be synthesized from the propargyl alcohol **3** which could, in turn, be prepared from the homoallylic alcohol **4** derived from pentane-1,5-diol (**5**).



Scheme 1 Retrosynthetic analysis of psiAβ (**2**)

Our synthesis (Scheme 2) was initiated by protection of one hydroxyl group of pentane-1,5-diol (**5**) by reaction with PMBCl and NaH to form ether **6**. The latter was oxidized with PCC, and the corresponding aldehyde underwent stereoselective Keck allylation[6] with allyl(tributyl)stannane in the presence of (*R*)-BINOL and $Ti(O\textit{i}\text{-}Pr)_4$ to produce the chiral homoallylic alcohol **4** (97% ee). The free hydroxyl group of **4** was protected with TBDMSCl, and ether **7** was subjected to hydroboration[7] using $BH_3{\cdot}SMe_2$ and $NaOH/H_2O_2$ to yield primary alcohol **8**. Alcohol **8** was oxidized with PCC, and the generated aldehyde was subjected to an asymmetric alkynylzinc addition[8] [Et_2Zn, (*S*)-BINOL, $Ti(O\textit{i}\text{-}Pr)_4$, PhOH] to produce propargyl alcohol **3** (92% de). The hydroxyl group of **3** was protected as its MOM ether, and the PMB ether group of **9** was deprotected to give alcohol **10**. The TBS ether group of **10** was subsequently removed to furnish diol **11**. TEMPO–bis(acetoxy)iodobenzene (BAIB) oxidation[9] of this 1,5-diol afforded lactone **12**, which was subjected to hydrogenation using Lindlar's catalyst to produce *cis*-olefin **13**.[10] Removal of the MOM ether group of **13** with DMS and $BF_3{\cdot}OEt_2$ yielded the target compound **2**, whose physical and spectroscopic properties were found to be identical to those reported for the natural product. The specific rotation of the naturally occurring compound was reported as $[\alpha]_D^{30}$ +63.7 (*c* 0.0042, MeCN)[2] and that of our synthetic compound was found to be $[\alpha]_D^{25}$ +60.8 (*c* 0.25, $CHCl_3$).

In conclusion, we have developed a stereoselective total synthesis of psiAβ, a sporogenic psi factor of the fungus *Aspergillus nidulans*, by applying a Keck allylation, an asymmetric alkynyl zinc addition, and a TEMPO–BAIB oxidation as the key steps.

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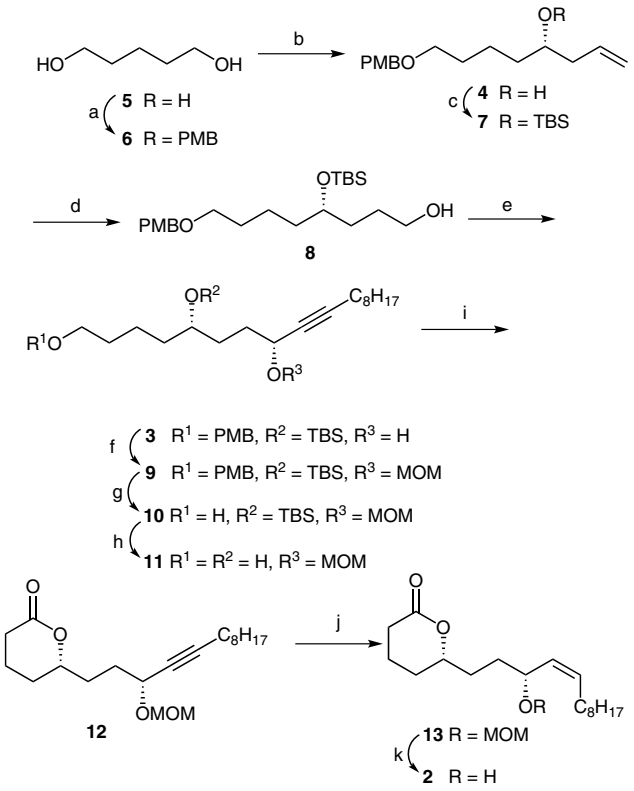

Scheme 2 Stereoselective synthesis of psiAβ (**2**). *Reagents and conditions*: (a) NaH, PMBCl, dry THF, 0 °C to r.t., 3 h, 91%; (b) (i) PCC, CH_2Cl_2, 0 °C to r.t., 2 h; (ii) Ti(O*i*-Pr)$_4$, (*R*)-BINOL, allyl(tributyl)stannane, 4 Å MS, dry CH_2Cl_2, 0 °C, 25 h, 78% (97% ee); (c) TBDMSCl, imidazole, DMAP, dry DMF, 0 °C to r.t., 2 h, 93%; (d) BH_3·SMe_2, dry THF, 0 °C to r.t., 2 h, NaOH/H_2O_2, 80%; (e) (i) PCC, CH_2Cl_2, 0 °C to r.t., 2 h; (ii) Et_2Zn, (*S*)-BINOL, Ti(O*i*-Pr)$_4$, PhOH, 4 h, 90% (92% de); (f) MOMCl, EtN*i*-Pr_2, dry CH_2Cl_2, 0 °C to r.t., 5 h, 88%; (g) DDQ, CH_2Cl_2–H_2O (19:1), 0 °C to r.t., 4 h, 82%; (h) TBAF, dry THF, 1 h, 89%; (i) TEMPO–BAIB, dry CH_2Cl_2, 0 °C to r.t., 4 h, 79%; (j) Lindlar's catalyst, EtOAc, H_2, r.t., 1 h, 88%; (k) DMS, BF_3·OEt_2, –10 °C, 1 h, 89%.

The Spectral Data of some Selected Compounds

Compound **4**: colorless liquid; $[\alpha]_D^{25}$ –12.9 (*c* 0.25, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.27 (2 H, d, *J* = 8.0 Hz), 6.68 (2 H, d, *J* = 8.0 Hz), 5.85–5.75 (1 H, m), 5.15–5.08 (2 H, m), 4.42 (2 H, s), 3.79 (3 H, s), 3.65–3.58 (1 H, m), 3.42 (2 H, t, *J* = 7.0 Hz), 2.29–2.24 (1 H, m), 2.14–2.08 (1 H, m), 1.55–1.38 (4 H, m), 1.34–1.28 (2 H, m). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 159.1, 134.0, 130.2, 129.1, 118.0, 113.9, 72.7, 70.1, 69.9, 55.1, 42.0, 36.8, 29.6, 22.1. ESI-MS: *m/z* = 265 $[M + H]^+$. Anal. Calcd (%) for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.67; H, 9.17. ESI-HRMS: *m/z* calcd for $C_{16}H_{25}O_3$ $[M + H]^+$: 265.17982; found: 265.17974.

Compound **9**: pale yellow liquid; $[\alpha]_D^{25}$ –6.3 (*c* 0.25, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.28 (2 H, d, *J* = 8.0 Hz), 6.88 (2 H, d, *J* = 8.0 Hz), 4.93 (1 H, d, *J* = 9.0 Hz), 4.59 (1 H, d, *J* = 9.0 Hz), 4.42 (2 H, s), 4.32–4.28 (1 H, m), 3.81 (3 H, s), 3.72–3.68 (1 H, m), 3.42 (2 H, t, *J* = 7.0 Hz), 3.36 (3 H, s), 2.19 (2 H, t, *J* = 7.0 Hz), 1.78–1.20 (22 H, m), 0.92–0.82 (12 H, m), 0.04 (3 H, s), 0.03 (3 H, s). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 159.1, 130.9, 129.2, 113.8, 94.0, 86.2, 78.7, 76.2, 72.6, 72.1, 70.0, 55.2, 55.1, 36.9, 32.2, 31.8, 31.7, 29.9, 29.1, 29.0, 28.9, 26.0, 22.6, 22.0, 18.9, 14.1, –4.9. ESI-MS: *m/z* = 577 $[M + H]^+$. Anal. Calcd (%) for $C_{34}H_{60}O_5Si$: C, 70.78; H, 10.48. Found: C, 70.80; H, 10.50. ESI-HRMS: *m/z* calcd for $C_{34}H_{61}O_5Si$ $[M + H]^+$: 577.42828; found: 577.42837.

Compound **11**: pale yellow oil; $[\alpha]_D^{25}$ +1.6 (*c* 0.25, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.97 (1 H, d, *J* = 9.0 Hz), 4.59 (1 H, d, *J* = 9.0 Hz), 4.39–4.36 (1 H, m), 3.70–3.62 (3 H, m), 3.39 (3 H, s), 2.19 (2 H, t, *J* = 7.0 Hz), 1.90–1.43 (10 H, m), 1.38–1.20 (13 H, m), 0.82 (3 H, t, *J* = 7.0 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 94.0, 86.9, 78.1, 71.4, 71.3, 62.8, 55.5, 37.0, 33.1, 32.5, 32.0, 31.9, 29.1, 29.0, 27.9, 27.8, 22.7, 21.9, 18.8, 14.0. ESI-MS: *m/z* = 343 $[M + H]^+$. Anal. Calcd (%) for $C_{20}H_{38}O_4$: C, 70.13; H, 11.18. Found: C, 70.12; H, 11.20. ESI-HRMS: *m/z* calcd for $C_{20}H_{39}O_4$ $[M + H)^+$: 343.28429; found: 343.28425.

Compound **12**: yellow liquid; $[\alpha]_D^{25}$ +5.7 (*c* 0.25, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.97 (1 H, d, *J* = 9.0 Hz), 4.59 (1 H, d, *J* = 9.0 Hz), 4.40–4.29 (2 H, m), 3.39 (3 H, s), 2.64–2.41 (2 H, m), 2.20 (2 H, t, *J* = 7.0 Hz), 1.99–1.76 (4 H, m), 1.67–1.52 (2 H, m), 1.40–1.21 (14 H, m), 0.89 (3 H, t, *J* = 7.0 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 171.3, 93.8, 87.0, 80.0, 55.6, 31.8, 31.0, 29.1, 29.0, 28.8, 28.7, 28.6, 28.3, 27.9, 22.2, 18.1, 18.0, 14.0. ESI-MS: *m/z* = 339 $[M + H]^+$. Anal. Calcd (%) for $C_{20}H_{34}O_4$: C, 70.97; H, 10.12. Found: C, 70.95; H, 10.15. ESI-HRMS: *m/z* calcd for $C_{20}H_{34}O_4Na$ $[M + Na]^+$: 361.23493; found: 361.23499.

Compound **2**: colorless oil; $[\alpha]_D^{25}$ +60.8 (*c* 0.25, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.36–5.33 (1 H, m), 5.29–5.23 (1 H, m), 4.39–4.26 (2 H, m), 2.50–2.40 (2 H, m), 1.99–1.91 (2 H, m), 1.90–1.82 (2 H, m), 1.68–1.51 (6 H, m), 1.40–1.22 (12 H, m), 0.88 (3 H, t, *J* = 7.0 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 172.0, 130.2, 130.0, 80.8, 71.2, 32.6, 32.1, 32.0, 29.9, 29.7, 29.6, 27.9, 23.0, 18.9, 14.0. ESI-MS: *m/z* = 297 $[M + H]^+$. Anal. Calcd (%) for $C_{18}H_{32}O_3$: C, 72.93; H, 10.88. Found: C, 72.95; H, 10.85. ESI-HRMS: *m/z* calcd for $C_{18}H_{33}O_3$ $[M + H]^+$: 297.25807; found: 297.25797.

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References and Notes

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