# Enantioselective total synthesis of pteridic acid A†

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**Pteridic acid A, a potent plant growth promoter with auxin-like activity, was synthesized enantioselectively by using the Evans asymmetric aldol reaction as the key C–C bond forming step.**

In the course of screening for plant growth regulators produced by epiphytic microorganisms on live plants, Igarashi and co-workers have recently isolated two novel polyketidic acids, pteridic acids A (**1**) and B (11-*epi*-**1**), from the fermentation broth of *Streptomyces hygroscopicus* TP-A0451 isolated from the stems of the bracken *Pteridium aquilinum*, and determined their structures on the basis of spectroscopic analyses including HMBC and NOESY experiments (Fig. 1).[1] They both exhibited a potent promoting activity in the formation of adventitious roots in the hypocotyls of kidney beans comparable to that of indol-3-acetic acid (auxin) at a very low concentration of 1 nM. Our interest in the substantial biological roles of secondary metabolites of microbial origin in the natural ecosystem[2] as well as the complex molecular architecture of pteridic acids featuring a spiroacetal ring and eight stereogenic centers around it prompted us to embark on the total synthesis of pteridic acids. We describe herein the first enantioselective total synthesis of pteridic acid A (**1**).

Pteridic acid A (**1**) was divided retrosynthetically into four fragments, **2**, **3**, **4** and **5**, by cleaving the C4–C5, C7–C8 and C11–C12 bonds (Fig. 1). These C–C bonds were considered to be installable by the Wittig olefination, Evans aldol reaction and acetylenic coupling, respectively. To construct the C5–C11 portion of pteridic acid A (*i.e.* **9**, Scheme 1), our synthesis began with the Evans asymmetric aldol reaction between **3**[3] and **4**,[4] which produced a 13:1 mixture of **6a** and its (7α,8α)-diastereomer favoring the desired 8,10-*anti*-adduct (**6a**). The mixture was subjected to a three-step sequence consisting of stereoselective reduction to **6b** (stereoselectivity, 10:1),[5] conversion to acetonide **7** and finally reductive removal of the chiral auxiliary to give stereochemically homogeneous alcohol **8** after chromatographic purification (69% isolated yield from **6a**). The C7,C9-*anti* relative stereochemistry of **8** was confirmed by analyzing its $^{13}C$ NMR spectrum, in which the signals due to the quaternary carbon and the two methyl carbons of the acetonide moiety were observed at 100.6, 24.9 and 23.5 ppm respectively, in good accordance with the data for analogous 1,3-*anti*-diol acetonides.[6] Finally, the alcohol (**8**) was oxidized with Dess–Martin periodinane (DMP)[7] to give the C5–C11 fragment (**9**).

The preparation of the C12–C16 fragment (**5**) is shown briefly in Scheme 2. The hydroxyl group of known ester **10**[8] was protected

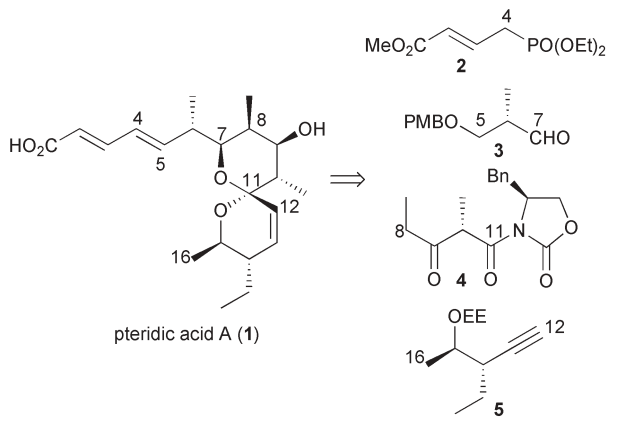
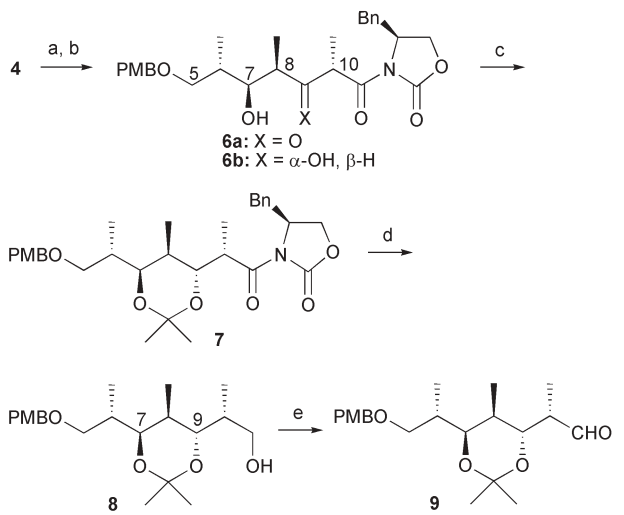
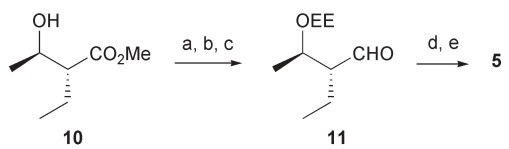



**Fig. 1** Retrosynthetic analysis of pteridic acid A.




**Scheme 1** *Reagents and conditions*: a) **3**, $Sn(OTf)_2$, $Et_3N$, $CH_2Cl_2$, −78 °C, 78%; b) $NaBH(OAc)_3$, AcOH, rt, 92%; c) $Me_2C(OMe)_2$, $TsOH·H_2O$, acetone, 30 °C, 96%; d) $LiBH_4$, MeOH, THF, rt, 78%; e) DMP, Py, $CH_2Cl_2$, rt, 94%.




**Scheme 2** *Reagents and conditions*: a) ethyl vinyl ether, PPTS, $CH_2Cl_2$, 0 °C; b) DIBAL, $CH_2Cl_2$, −78 °C; c) DMSO, $(COCl)_2$, $Et_3N$, $CH_2Cl_2$, −78 °C, 69% from **10**; d) $CBr_4$, $Ph_3P$, Py (4.2 eq.), $CH_2Cl_2$, 0 °C; e) *n*-BuLi, THF, −78 °C, 51% from **11**.

† Electronic supplementary information (ESI) available: $^1H$ NMR spectra for compounds **5**, **9**, **14a**, **14b**, **14c**, **15a**, **15b**, **15c** and **1**. See http://www.rsc.org/suppdata/cc/b4/b416309e/

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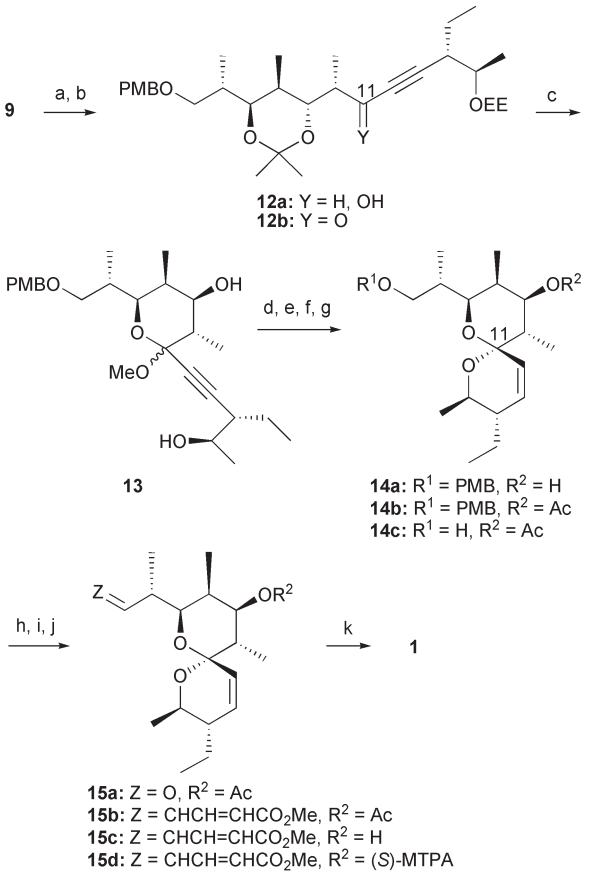


**Scheme 3** *Reagents and conditions*: a) **5**, *n*-BuLi, THF, −78 °C, 40%; b) DMP, Py, $CH_2Cl_2$, rt, 93%; c) CSA, $CH_2Cl_2$–MeOH (7.5:1), rt, 78%; d) $H_2$, Lindlar catalyst, 1-hexene–EtOAc (1:1), rt; e) PPTS, toluene, rt, 88% from **13**; f) $Ac_2O$, DMAP, Py, rt, quant.; g) DDQ, $CH_2Cl_2$–pH 7 phosphate buffer (10:1), 0 °C, 87%; h) DMP, Py, $CH_2Cl_2$, rt; i) **2**, LiHMDS, THF, −78 °C, 91% from **14c**; j) MeOH, $K_2CO_3$, rt, 83%; k) KOH, MeOH–$H_2O$ (2:1), rt, 99%.

as the ethoxyethyl ether and the ester group was reduced to give an alcoholic intermediate, which was then oxidized to aldehyde **11**. Dibromomethylenation of **11** in the presence of pyridine, proceeded cleanly to give the corresponding dibromo-olefin intermediate. The presence of pyridine was essential in this reaction because its absence caused complete deprotection of the ethoxyethyl protecting group. Finally, dehydrobromination of the olefinic intermediate furnished the C12–C16 fragment (**5**).

The acetylide anion prepared from **5** was added to aldehyde **9** to give **12a** as a mixture of epimeric alcohols at C11 (Scheme 3). The chemical yield of this step was moderate (40%) owing to the concurrent β-elimination of **9** leading to the corresponding α,β-unsaturated aldehyde. After oxidation of **12a** to acetylenic ketone **12b**, the product was exposed to acidic conditions (CSA, $CH_2Cl_2$–MeOH) to remove the two acetal protecting groups, which brought about concomitant cyclic acetal formation to give **13** as a 3:1 epimeric mixture. Catalytic semi-hydrogenation of **13** and subsequent spiroacetal ring-formation using PPTS in toluene gave **14a** as a single stereoisomer. The stereochemistry of the spiro-center of **14a** was tentatively assigned based on the anomeric effect. Conversion of **14a** into the corresponding acetate (**14b**) was followed by oxidative removal of the PMB protecting group (DDQ, $CH_2Cl_2$–pH 7 phosphate buffer), which caused partial epimerization at the spiro-center, affording an inseparable 6:1 mixture of **14c** and its C11-epimer. The Dess–Martin oxidation of the epimeric mixture containing **14c** as the major component (**14c→15a**) was followed by four-carbon chain-elongation using the C1–C4 fragment (**2**) (**15a→15b**) and subsequent removal of the acetyl protecting group to yield a mixture of hydroxy esters, from which **15c** could be isolated by $SiO_2$ chromatography (76% yield from **14c**).[9] The $^1$H NMR spectrum of **15c** was identical to that of an authentic sample previously prepared by Igarashi *et al.* from natural pteridic acid A.[1] Finally, hydrolysis of the methyl ester completed the enantioselective total synthesis of pteridic acid A (**1**) {$[\alpha]^{24}_D$ + 24 (*c* 0.15, $CHCl_3$); lit.[1] $[\alpha]^{24}_D$ + 22.3 (*c* 1.0, $CHCl_3$)}.[10] The $^1$H and $^{13}$C NMR spectra of **1** were identical to those of natural pteridic acid A. The enantiomeric homogeneity of our synthetic pteridic acid A was assured by comparison of the $^1$H NMR spectra of (*S*)-MTPA-ester samples (**15d**) prepared from synthetic **15c** and from authentic **15c** which was previously derived from natural pteridic acid by Igarashi *et al.*[1]

In conclusion, the first total synthesis of (+)-pteridic acid A (**1**) was accomplished in 8.4% overall yield from the known oxazolidinone derivative (**4**) through 16 steps including the Evans asymmetric aldol reaction, acetylenic coupling and Wittig olefination as the key C–C bond forming steps, which confirmed the structure of **1** including its absolute configuration. Attempts to obtain pteridic acid B[9] and to apply the present synthetic strategy to the synthesis of structurally related natural products such as halichoblelide (a cytotoxic macrolide)[11] and elaiophylin (an antibiotic)[8,12] are now underway.

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9 The silica gel column chromatography (hexane/ethyl acetate, 50:1→10:1) gave pure **15c** (76% isolated yield) and a mixture of **15c** and 11-*epi*-**15c** originating from 11-*epi*-**14c**, which in turn was produced by partial epimerization of the spiro-center during the conversion of **14b** into **14c**. The mixture of esters could be saponified with KOH–$H_2O$–MeOH into a mixture of pteridic acids A (**1**) and B (**2**). Although the

presence of pteridic acid B in the saponification product mixture was assured by the $^1$H NMR spectrum of the mixture, we were unable to fully purify **2** because of its scarcity.

10 Igarashi *et al.* originally reported the specific rotation value of pteridic acid A to be −22.3.[1] However, they recently informed us that the *minus* sign was a typing error and the real sign was *plus* (+). They also informed us that the absolute configuration of the C10-stereogenic center of pteridic acids depicted in their paper[1] was erroneous and the correct stereochemistry should be represented by structure **1** shown in this paper.

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