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Total Synthesis of Pteridic Acid A

J. S. Yadav,* V. Rajender, and Y. Gangadhara Rao

Organic Chemistry Division-1, Indian Institute of Chemical Technology, Hyderabad 500 007, India

yadavpub@iict.res.in

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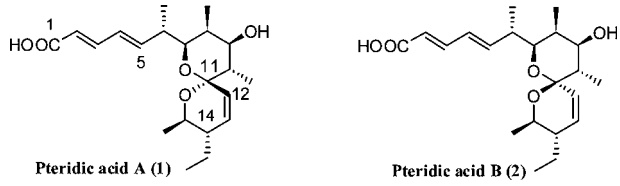
ABSTRACT

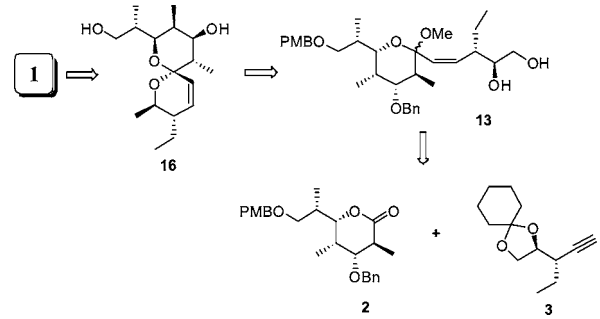


A convergent approach to the total synthesis of pteridic acid A, having potent plant growth regulator activity, is described. Key steps include the desymmetrization of bicyclic olefin with Brown's chiral hydroboration, acid-mediated spiroketalization, and zirconium-catalyzed ethylmagnesation protocol to install the ethyl stereocenter at C14.

Pteridic acid A, a spirocyclic polyketide natural product, was isolated by the Igarashi group[1] from the fermentation broth of *Streptomyces hygroscopicus* TP-A0451 obtained from the stems of the bracken *Pteridium aquilinum*, collected in Toyama, Japan. It induces the formation of adventitious roots in hypocotyls of kidney beans (at 1 nM concentration) as effectively as auxins[2] (indole-3-acetic acid), a natural phytohormone. The structure of pteridic acid was determined to be a spiroketal from extensive spectroscopic studies including HMBC and NOESY experiments. Structurally, pteridic acids A and B are epimers, differing at the C11 spiro center, and possess a highly substituted dioxaspiro[5.5]undecene ring system comprising seven stereo centers along with a conjugated diene carboxylic acid side chain at C7, which accommodates one more chiral center.

First total synthesis of pteridic acid A was reported by Kuwahara et al.[3] in 2005 followed by the Paterson group[4] and recently by the Dias group.[5] The earlier synthetic efforts toward pteridic acid syntheses relied on auxiliary/boron-mediated aldols to construct the polyketide core, Frater or Seebach alkylation, and boron-mediated aldols to install the ethyl-bearing C14 stereocenter. As part of our studies on the synthesis of spirocyclic natural products[6] and macrolides containing polyketide units by exploiting a desymmetrization strategy,[7] we present a novel strategy for pteridic acid A, radically different from those reported so far.

Scheme 1. Retrosynthetic Analysis of Pteridic Acid A (**1**)



Retrosynthetically (Scheme 1), we envisaged that **1** could be prepared by short sequential manipulations of diol **16**, embedded with all of the required stereocenters, and the diol **16** in turn could be generated by acid-mediated spiroketal-

(1) Igarashi, Y.; Iida, T.; Yoshida, R.; Furumai, T. *J. Antibiot.* **2002**, *55*, 764–767.

(2) (a) Igarashi, Y.; Yoshida, R.; Furumai, T. *Shokubutsu no Seicho Chosetsu* **2002**, *37*, 63–68. (b) Igarashi, Y.; Iida, T.; Sasaki, T.; Saito, N.; Yoshida, R.; Furumai, T. *Actinimycetologica* **2002**, *16*, 9–13.

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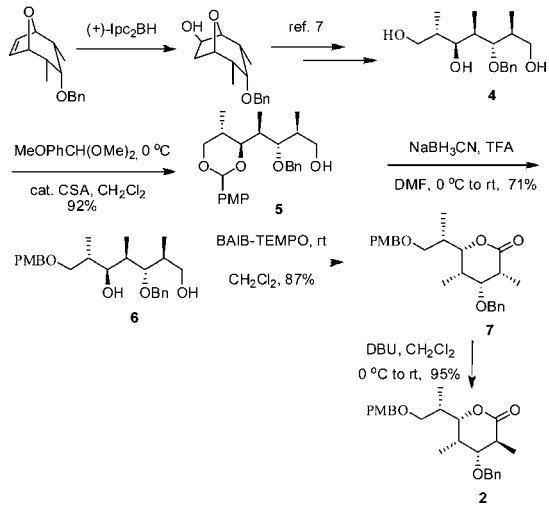
ization of hemiacetal **13**. Intermediate **13** could be obtained by assembling lactone **2** (C5−C11) and alkyne **3** (C12−C15).

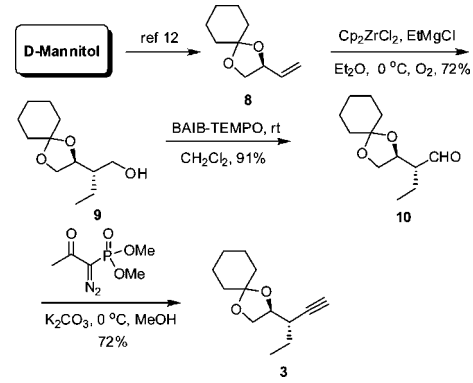
Scheme 2. Synthesis of Lactone **2**



As outlined in Scheme 2, the C5−C11 segment **2** was prepared mainly on the basis of desymmetrization of bicyclic olefin using Brown's chiral hydroboration via known triol **4**, which was extensively utilized as a building block for the synthesis of many natural products containing polypropionate units in our laboratory.[7] Synthesis of lactone **2** was commenced with the conversion of triol **4** to acetal **5** using anisaldehyde dimethyl acetal[8] and catalytic CSA. Reductive opening of acetal with $NaBH_3CN$[9] led to the 1,5-diol **6** (71% yield). The resulting 1,5-diol was subjected to oxidative lactonization in the presence of BAIB-TEMPO[10] to obtain lactone **7** (87% yield). Epimerization of lactone **7** at the C2 position by exposure to a stoichiometric amount of DBU[7b] completed the construction of the key Prelog−Djerassi-type lactone **2**.

The synthesis of the C12−C15 segment (Scheme 3) began with the installation of the crucial ethyl center at C14 by employing a zirconium-catalyzed carbomagnesation protocol developed by Hoveyda.[11] Thus the treatment of olefin[12] **8** with EtMgCl and 5 mol % of Cp_2ZrCl_2 at room temperature

Scheme 3. Synthesis of Alkyne **3**



for 12 h followed by quenching of the ethylmagnesation product with O_2 resulted in the formation of alcohol **9** (72%) as a single diastereomer. Though terminal alkenes are not subject to strict conformational control, exclusive formation of the diastereomer is due to bulky cyclohexylidene protection adjacent to the site of addition in olefin **8**. Having successfully installed the C14 ethyl center using an efficient protocol, we next proceeded to synthesize the alkyne functionality by oxidation of alcohol **9** with BAIB-TEMPO to afford aldehyde **10** (91% yield), which was converted to alkyne **3** (72%) by employing Ohira−Bestmann reagent.[13]

As our initial objective to synthesize the pteridic acid A through the assemble of the lactone **2** with vinyl iodide **11** (prepared from aldehyde **10** using Stork and Zhao protocol) using *n*-BuLi and *i*-PrMgBr[14] met with failure and ended up with doubly vinylated product (in minor quantities) along with unsaturated lactone (in major quantities). When we tried the coupling by transmetalation of Li to Mg using *t*-BuLi-$MgBr_2$[15] at −136 °C (Liq N_2-pentane bath), it resulted in dehydrohalogenation of vinyl iodide along with unreacted lactone (Scheme 4).

The failures of our initial attempts forced us to revise the coupling strategy (Scheme 5) in which the alkyne **3** was chosen as a coupling partner. Thus, treatment of lactone **2** with lithium acetylide[16] of **3** at −78 °C afforded lactol. Exposure of this crude lactol to a catalytic amount of CSA in MeOH resulted in the formation of hemiacetal **12** with concomitant deprotection of the cyclohexylidene acetal.

Next the hemiacetal **12** was subjected to partial hydrogenation using Lindlar's catalyst to establish the *Z*-alkene functionality in **13** (92%). Our next key task en route to the synthesis of pteridic acid A, spiroketalization was achieved under mild acidic conditions. To our delight, the NMR

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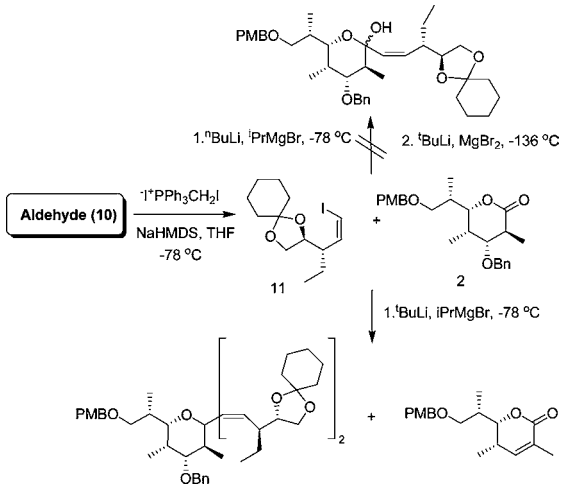
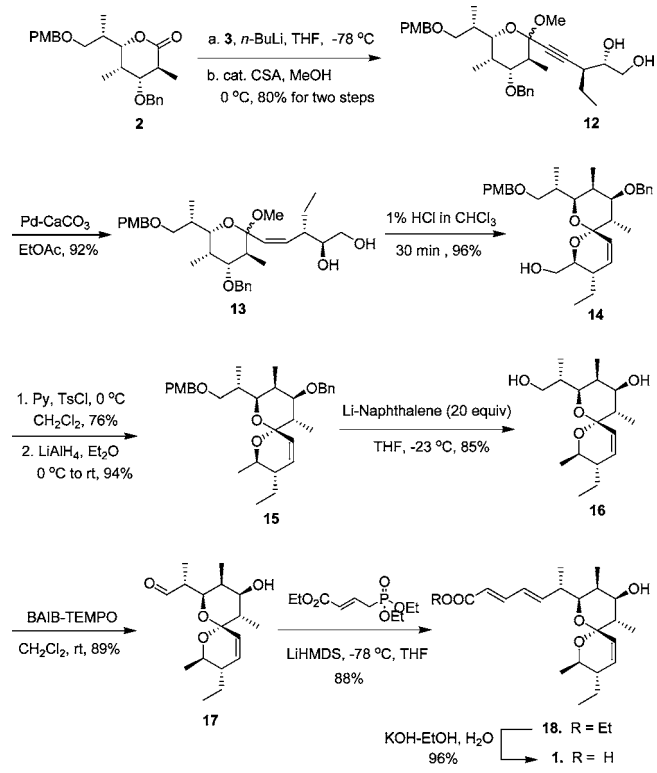
Scheme 4. Initial Attempt To Couple Fragments **2** and **11**



Scheme 5. Synthesis of Pteridic Acid A (**1**)



sample of hemiacetal **13** in $CDCl_3$ completely converted to spiro compound **14**, which was confirmed by ^{1}H and ^{13}C NMR. Thus, treatment of **13** in 1% HCl in $CHCl_3$ resulted in the formation of spiro compound **14** as a single diastereomer (96%), which can be explained through double anomeric effect,[17] and appearance of the ^{13}C signal (96.89 ppm) of the spiro carbon comparable to that of natural pteridic acid A (96.86 ppm) confirmed the required stereochemical outcome.

At this juncture, it is necessary to establish the methyl chiral center at C15. To this end, the primary alcohol in spiroketal **14** was transformed to a methyl group by a tosylation−reductive elimination sequence to furnish deoxygenated spiroketal **15**. The deprotection of both PMB and benzyl ethers by using excess Li-naphthalenide[18] (20 equiv) afforded diol **16** (91%) and minor product epimerized at the spirocyclic carbon to an extent of 2−3%.[3b] Selective oxidation of primary alcohol in diol **16** to aldehyde **17** was achieved with BAIB-TEMPO in CH_2Cl_2 at room temperature (89% yield), and appendage of the conjugated diene ester to the aldehyde using known phosphonate ester through HWE olefination furnished the corresponding conjugate ester **18** (88% yield). Finally, saponification of ethyl ester **18** with KOH in EtOH accomplished the synthesis of pteridic acid A (96%), whose spectral and analytical data were in good agreement with the reported values.

In conclusion, the total synthesis of pteridic acid A has been achieved. Key features of this synthesis are efficient desymmetrization strategy to construct the polyketide core, zirconium-catalyzed carbomagnesation protocol to install the C14 ethyl stereocenter, and an effective spiroketalization under mild acidic conditions. The 13-step longest linear sequence proceeding from triol **4** gave an overall yield of 17.4%.

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Supporting Information Available: Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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