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Five Easy Pieces. The Total Synthesis of Phosphoiodyn A (and Placotylene A)

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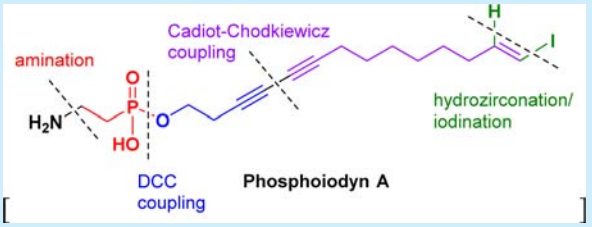
Supporting Information

ABSTRACT: The convergent total synthesis of the marine natural product phosphoiodyn A, a nanomolar agonist of human peroxisome proliferator-activated receptor delta (hPPARδ), was achieved in five steps total from commercially available and inexpensive starting materials. The synthesis relies on the unprecedented regioselective hydrozirconation of a terminal acetylene in the presence of a conjugated 1,3-diyne and on ammonolysis of a β-chlorophosphonic acid monoester. The scheme also provides the newly isolated placotylene A, an inhibitor of bone marrow-derived macrophage (BMM) differentiation.



Both polyacetylenes[1,2] and iodo olefins[3] are well represented among biologically active marine natural products. However, the phosphoiodyns (**1A** and **1B**)[4] and the placotylenes (**2A** and **2B**)[5] are the only natural products reported to date that contain both functionalities.[6]

The phosphoiodyns were described in early 2013 as isolates from *Placospongia* sp. which had been collected by SCUBA in the South Sea, Korea.[4a] A 0.94-kg dry-weight sample of the marine sponge afforded, after fractionation and reversed phase HPLC, 4.5 mg of phosphoiodyn A and 8.8 mg of phosphoiodyn B. In an *in vitro* transfection assay, phosphoiodyn A showed itself to be a potent and selective agonist (EC_{50} 23.7 nM) of human peroxisome proliferator-activated receptor delta (hPPARδ), a transcription factor involved in lipid and glucose metabolism. Agonists of hPPARδ are of interest as leads for the development of drugs for metabolic diseases such as obesity and type II diabetes.[7] Phosphoiodyn B was reported to be inactive in this screen.

In 2014, the originally assigned phosphoiodyn structures, a β-hydroxyphosphonic acid and a hydroxyethyl phosphate, were revised to the corresponding β-aminophosphonic acid and aminoethyl phosphate structures shown in Figure 1.[4b] Derivatives of 2-aminoethylphosphonic acid (AEP, **3a**) are commonly found in marine sources.[8] However, there are only a few examples of the synthesis of a monoester of AEP.[9]

Inspired by the biological activity of phosphoiodyn A and the challenge of preparing this target by a very short and efficient scheme, we considered the availability of starting materials that might offer ideal or nearly ideal functional group patterns. A quick analysis revealed that a synthesis that relied on ammonolysis[10] of an ester of 2-chloroethylphosphonic acid (**3b**) would be shorter (total steps) than one that used amino phosphonic acid **3a**; furthermore, it would be equally convergent. Together, the commercially available acid **3b**, 3-butyn-1-ol (**4**), and 1,9-decadiyne (**5**) contain all of the carbon atoms and all of the functional group equivalents, appropriately

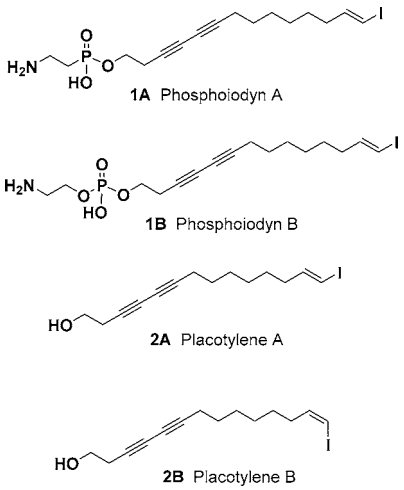


Figure 1. Phosphoiodyn and placotylene marine natural products.

positioned, for the construction of the target (**1A**); see Figure 2.

The synthesis of phosphoiodyn A from the three starting materials would require suitable modification of each segment: activation of the phosphonic acid **3b** for the esterification, functionalization of homopropargyl alcohol **4** in order to ensure heterocoupling for triyne synthesis, and hydroiodination of one of the alkyne bonds derived from diyne **5** for elaboration of the final structure. The hydroiodination would necessarily be effected in the presence of at least one additional alkyne bond. Ordering these transformations for an efficient plan led us to Scheme 1.

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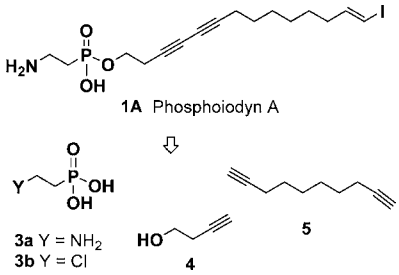
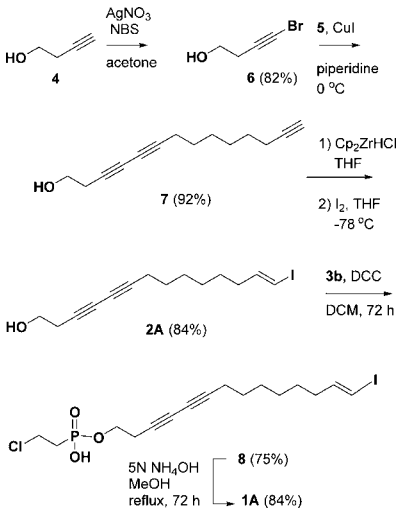


Figure 2. Phosphoiodyn A and selected commercially available starting materials for its synthesis.

Scheme 1. Total Synthesis of Phosphoiodyn A



Synthesis of the key intermediate **7** was accomplished in two steps. 4-Bromo-3-butyn-1-ol (**6**) was prepared by the literature method.[11] Then a Cadiot−Chadkiewicz reaction[12] with excess 1,9-decadiyne (**5**) gave the easily isolated triynol.

The challenge then was to selectively convert the terminal alkyne bond of triynol **7** to an (*E*)-iodoolefin. A search of the literature revealed no examples of the hydroiodination (or hydroboration, hydroalumination, hydrostannylation, or hydrozirconation) of an isolated alkyne in the presence of a 1,3-diyne. Therefore, we set out to find conditions for the desired transformation.

Attracted by the ease of handling of the Schwartz reagent, we hoped to capitalize on the established steric demand of this transition metal hydride.[13] It seemed reasonable that the Schwartz reagent would prefer to react at the least hindered unsaturation.

In the event, hydrozirconation/iodination[14] was accomplished with the Schwartz reagent prepared by Negishi's procedure.[15] Thus, triynol **7** was converted cleanly to the iodoolefinic diynol **2A** in 84% yield. Even with an excess of the Schwartz reagent, we saw no modification of the diyne system.

It remained then to prepare the aminophosphonate derivative of alcohol **2A**. North et al. had reported that a standard DCC/DMAP procedure was effective for the monoesterification of a phosphonic acid.[16] In our hands, a DCC protocol cleanly converted alcohol **2A** to the chlorophosphonic acid ester **8** in 75% yield. Completion of the synthesis was achieved by submitting a solution of this intermediate to NH_4OH in a pressure vessel. The natural product, phosphoiodyn A (**1A**), was isolated in 85% yield by precipitation.

During the course of this work, the natural products placotylenes A (**2A**, our synthetic intermediate, Scheme 1) and B (**2B**) were discovered.[5] At 10 μM, placotylene A inhibited osteoclastogenesis stimulated by the receptor activator of nuclear factor-κB ligand (RANKL) in bone marrow derived macrophages (BMMs). Compounds with this activity are thought to have potential in the remediation of bone loss. Activity in this screen was not observed for placotylene B.

The total synthesis of placotylene A (**2A**) was achieved in three steps and an overall yield of 63% from commercially available materials; the scheme features a regio- and stereoselective hydrozirconation of an isolated, terminal alkyne in the presence of a disubstituted diyne moiety. Conversion of this natural product to the more complex phosphoiodyn A (**1A**) required an additional two steps for an overall yield of 41%.

Phosphoiodyn A and placotylene A have potential as novel pharmaceutical lead compounds.[17] Their ready availability and the prospect of analog synthesis should facilitate studies of both hPPARδ agonist and RANKL inhibitor activities.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02642.

Full experimental procedures, copies of the 1D and 2D NMR spectra and infrared spectra (PDF)

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Notes

The authors declare no competing financial interest.

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