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Four-Step Total Synthesis of Selaginpulvilin D

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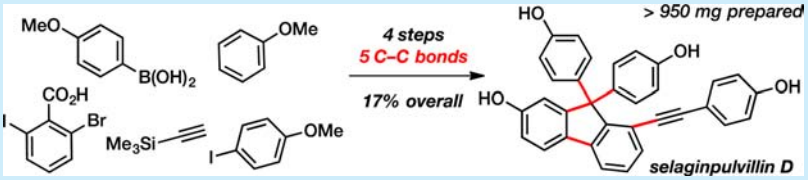
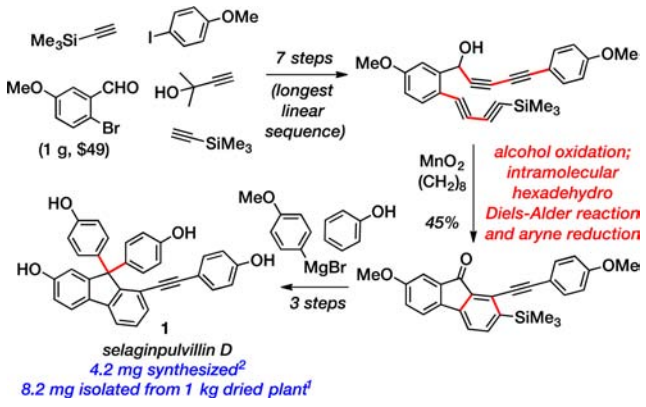
Supporting Information



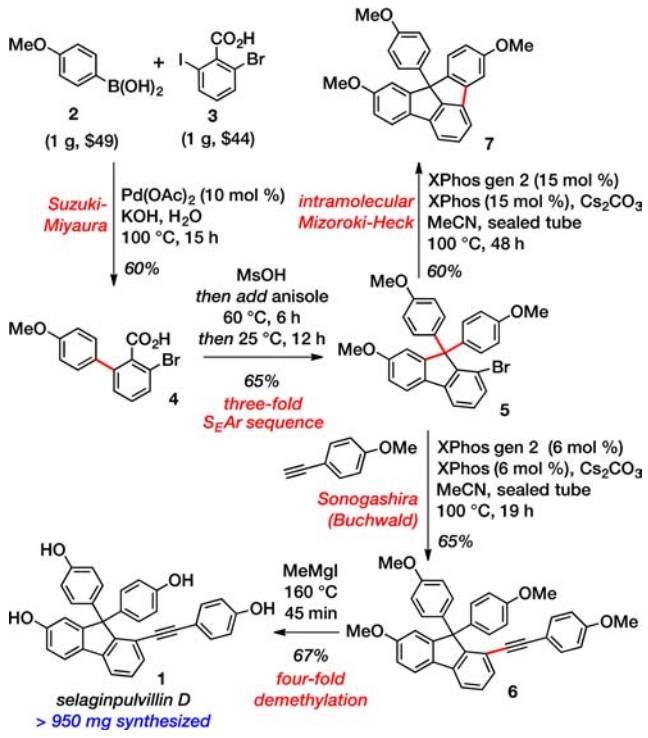
ABSTRACT: An extremely concise total synthesis of a potent phosphodiesterase-4 inhibitory natural product, selaginpulvilin D, is reported. The synthesis features a one-pot, 3-fold electrophilic aromatic substitution sequence to assemble a 9,9-diarylfluorene core. The approach allows access to useful quantities of a selaginpulvilin natural product for the first time.

The selaginpulvilin family is a small group of 1-arylethynyl-9,9-diarylfluorene natural products that are likely responsible for the anti-inflammatory properties of *Selaginella pulvinata* (Hook. et Grev.) Maxim. (Selaginellaceae), a plant used widely in traditional Chinese medicine.[1] One kilogram of dried whole plant material furnished 8.2 mg of selaginpulvilin D (**1**).[1] Karmakar and Lee very recently reported an elegant, 11-step total syntheses of **1** (summarized in Scheme 1, detailed in the SI) and its 2-methyl analogue, selaginpulvilin C. Lee's synthesis showcases a reductive intramolecular hexahydro Diels–Alder reaction to assemble the fluorenone core of the natural product, ultimately providing 4.2 mg of the natural product **1**.[2] The publication of the Lee synthesis prompts us to report the first practical synthesis of **1**, which deploys precursors of similar cost[3] and structural complexity to those in the Lee study yet delivers *almost 1 g of the natural product in only four steps*.

Scheme 1. Summary of Karmakar and Lee's 11-Step Total Synthesis of Selaginpulvilin D (1)[2,3]



Scheme 2. Four-Step Total Synthesis of Selaginpulvilin D (1)[3,9]



The publication of the Lee synthesis prompts us to report the first practical synthesis of **1**, which deploys precursors of similar cost[3] and structural complexity to those in the Lee study yet delivers *almost 1 g of the natural product in only four steps*.

Our synthesis (Scheme 2) commences with a Suzuki–Miyaura coupling of 4-methoxyphenylboronic acid **2** with 2-bromo-6-iodobenzoic acid **3** in an aqueous medium[4] to generate disubstituted 2-phenylbenzoic acid **4**. A selective single cross-coupling necessitated the use of the bromoiodoarene, since the corresponding diiodide underwent selective 2-fold couplings.[5]

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On warming in methanesulfonic acid, intramolecular S_EAr reaction gave the fluorenone, which could be isolated (see the SI) but was, more conveniently, converted in situ into the 1-bromo-9,9-diarylfluorene **5** simply by addition of anisole. Intramolecular S_EAr reactions of 2-arylbenzoic acids to fluorenones are well established,[6] as are 2-fold intermolecular S_EAr sequences to convert fluorenones into 9,9-diarylfluorenes.[7] Nonetheless, the telescoping of these two classical transformations into a one-flask operation is unprecedented.[8]

The third step of the synthesis was a challenging Sonogashira coupling to install the 1-arylethynyl fragment through reaction of sterically encumbered bromide **5** with 4-(methoxyphenyl)-acetylene.[10] Only Buchwald's second-generation XPhos pre-catalyst[11,12] was fruitful, and even then only with a high concentration of the terminal alkyne cross-coupling partner. At lower concentrations, the desired Sonogashira coupling product **6** was generated as a mixture with intramolecular Mizoroki–Heck[13] product **7**; in the absence of alkyne coupling partner, fused pentacycle **7** was formed exclusively.

The natural product **1** was accessed by 4-fold demethylation of the Sonogashira coupling product **6** by heating with neat methylmagnesium iodide at 160 °C.[14] More conventional protocols (BBr_3, RSH/$AlCl_3$) gave mixtures of products resulting from additions to the alkyne.

In summary, an uncommonly short total synthesis of the natural product selaginpulvilin D has been completed. In comparison with the recently reported approach,[2] the present synthesis boasts a dramatic reduction in step count, a significant increase in overall percentage yield (4.4% to 17%) and access to a much larger amount of the natural product. The provision of useful quantities of selaginpulvilin D through chemical synthesis prevents the need for large-scale harvesting of *S. pulvinata* (some 117 kg of dry plant would be needed to produce the same amount of material prepared so far). This synthetic route should be amenable not only to much larger quantities of the natural product but also to the preparation of the remaining members of the selaginpulvilin family, along with many analogues and derivatives.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03793.

Experimental procedures, product characterizations, ^1H and ^{13}C and NMR spectra of new compounds, spectroscopic comparisons of the isolated and synthesized natural product, and a detailed synthetic scheme for the previously published total synthesis (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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(8) The same overall transformation can be achieved through a two-fold nucleophilic addition to an ester to generate a tertiary alcohol, which in a separate step can undergo S_EAr cyclization through treatment with acid. See, for example: Jacob, J.; Sax, S.; Piok, T.; List, E. J. W.; Grimsdale, A. C.; Muellen, K. *J. Am. Chem. Soc.* **2004**, *126*, 6987–6995.

(9) Each of the four steps of the total synthesis depicted in Scheme 2 was performed using more than 1 g of precursor.

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