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Total Synthesis of Selaginpulvilin C and D Relying on *in Situ* Formation of Arynes and Their Hydrogenation

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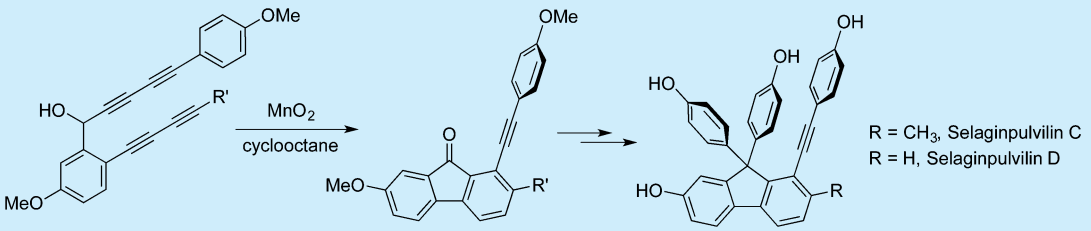
Supporting Information



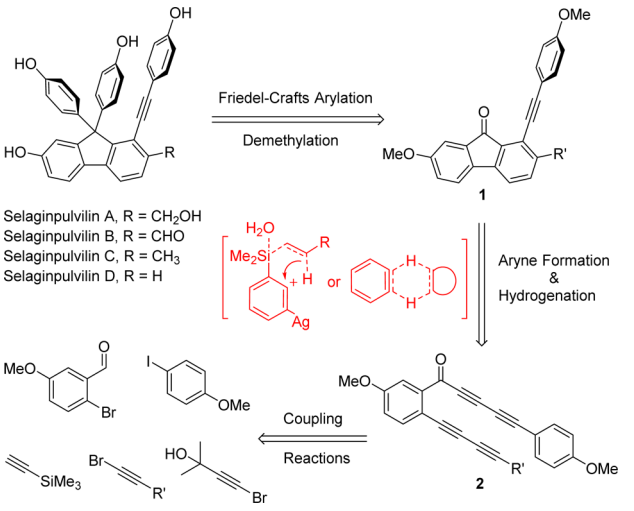
ABSTRACT: The total syntheses of selaginpulvilins C and D is described. The key strategy for the construction of the core fluorene moiety involves in situ formation of an aryne intermediate followed by its formal hydrogenation. The precursor tetraynes that undergo aromatization via hexadehydro Diels–Alder reaction were prepared from readily available building blocks through typical alkyne-coupling reactions.

Selaginpulvilins A–D that contain a novel 9,9-diphenyl-1-(phenylethynyl)-9*H*-fluorene framework were reported by Yin and co-workers in 2014.[1] The structural assignment of these tetraphenolic compounds was secured by spectroscopic, chemical, and single-crystal X-ray diffraction analyses. These unprecedented natural products were isolated from *Selaginella pulvinata* (Hook. et Grev.) Maxim. (Selaginellaceae), which has been widely used in traditional Chinese medicine.[2] The activity-guided bioassays of ethanolic extracts of *S. pulvinata* containing selaginpulvilins A–D and other constituents showed significant inhibitory activities (IC_{50} values of 0.11–5.13 μM) against phosphodiesterase-4 (PDE4).

The important biological profiles of selaginpulvilins in combination with their novel structural features make them highly attractive targets for total synthesis, which will also provide an opportunity to develop a range of related structures for further biological activity–relationship studies. In terms of designing an effective synthetic approach, we envision that 9,9-diphenyl substituents on the central fluorene substructure[3] of selaginpulvilins can be installed via double Friedel–Crafts arylations with precursor **1** (Scheme 1). In turn, the phenylethynyl-9*H*-fluorenone structure can be constructed from tetrayne **2** via a hexadehydro Diels–Alder reaction[4−6] (HDDAR) to form an aryne[7] intermediate followed by its formal hydrogenation via either intramolecular hydride transfer from a trialkylsilyl group followed by protonation[5c] or hydrogen transfer from cyclooctane.[4h] Finally, tetrayne **2** would be accessed from readily available arene and alkyne building blocks.

The preparation of tetrayne **2** commenced with a Sonogashira coupling of commercially available 2-bromo-5-methoxybenzaldehyde with (trimethylsilyl)acetylene to generate **3** (Scheme 2).[8] 4-(Methoxyphenyl)-1,3-diyne **4** was also prepared through a merger of 4-iodoanisole and (trimethylsilyl)acetylene, desilylation, and a Cadiot–Chodkiewicz coupling with 4-bromo-2-methylbut-3-yn-2-ol followed by removal of the acetone moiety to liberate a terminal alkyne under basic conditions. Generation of an acetylide from **4** and its addition to aldehyde **3** afforded alcohol **5**.

Scheme 1. Selaginpulvilin Retrosynthesis



Removal of the trimethylsilyl group from **5** followed by a copper-catalyzed coupling with bromoalkynes delivered tetraynes **7a–e**.

With these substrates for HDDAR in hand, we explored their conversion to the projected fluorenones. On the basis of the established protocol[5c] for intramolecular hydride transfer to an

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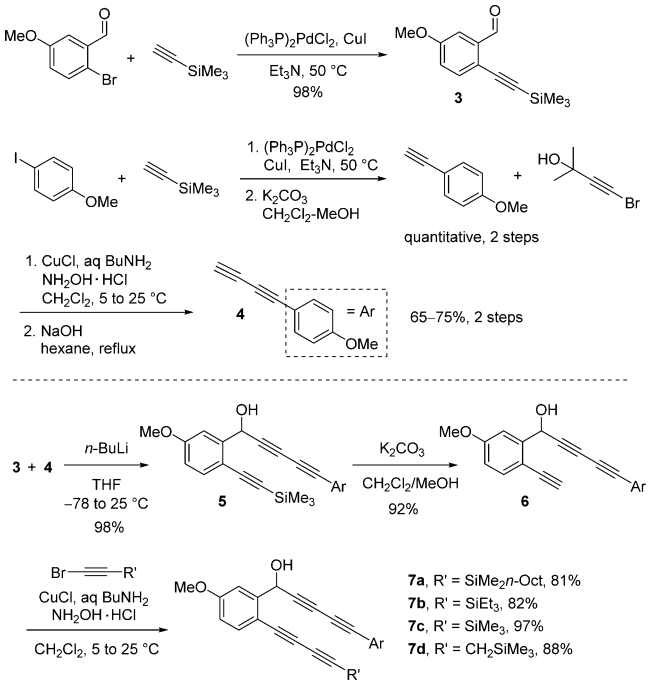
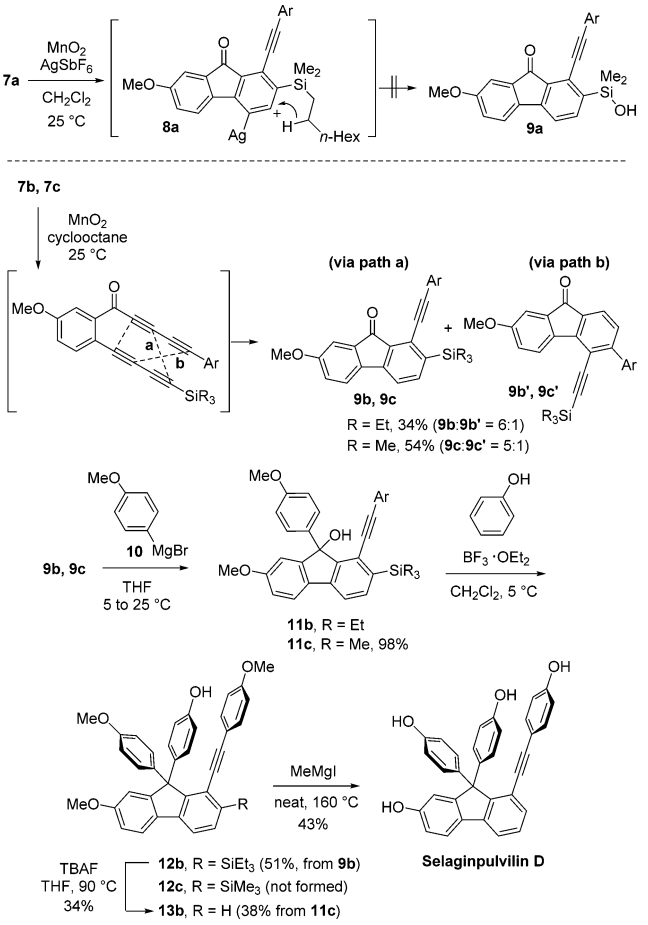
Scheme 2. Synthesis of Tetraynes



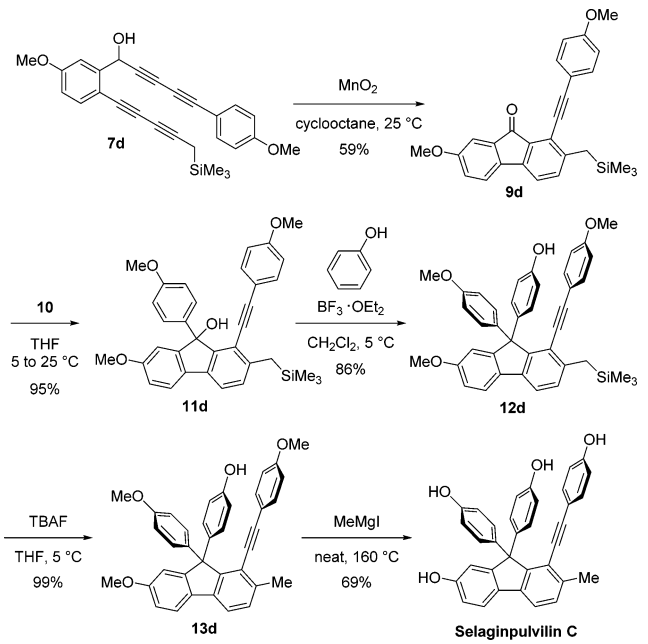
aryne species catalyzed by a silver catalyst, tetrayne **7a** was treated with MnO_2 at 25 °C in CH_2Cl_2 in the presence of $AgSbF_6$ (10 mol %) (Scheme 3). Unfortunately, substrate **7a** decomposed upon addition of $AgSbF_6$. Next, **7b** was oxidized with MnO_2 in cyclooctane as a source of hydrogen.[4h] Gratifyingly, desired compound **9b** was generated in 34% overall yield as a mixture of two isomers in a 6:1 ratio, the minor isomer of which was formed via the alternative mode of HDDAR. On the other hand, the corresponding trimethylsilyl-containing **7c** provided **9c** in 54% yield along with another isomer in a 5:1 ratio. Addition of anisole-based Grignard reagent **10** to ketone **9b** provided an adduct *tert*-alcohol **11b**, which was directly subjected to the known Friedel–Crafts arylation conditions to afford **12b** in 51% overall yield from **9b**.[9,10] Subsequent removal of the triethylsilyl group from **12b** was found to be recalcitrant. Treating **12b** with an excess amount of Bu_4NF at 90 °C afforded the corresponding desilylated product **13b**, *O*-trimethylselaginpulvilin D, in only 34% yield along with 22% recovered starting material **12b**. In stark contrast, the Friedel–Crafts arylation of trimethylsilyl-containing compound **11c** directly generated protodesilylated compound **13b** in 38% yield devoid of **12c** under otherwise identical conditions. The final cleavage of the methyl ethers with Me_3SiI[11] or BBr_3[12] afforded a mixture of several products of incomplete demethylation After much experimentation, it was found that treating **13b** with MeMgI in neat at 160 °C under reduced pressure delivered selaginpulvilin D.[13]

With the successful route in hand, synthesis of another congener of the same family, selaginpulvilin C, was attempted. The (trimethylsilyl)methyl-substituted tetrayne **7d** was proposed to be a good choice for this purpose. Treating **7d** with MnO_2 in cyclooctane at room temperature afforded fluorenone **9d**, which was reacted with Grignard reagent **10** to generate **11d** (Scheme 4). Subsequently, with the established Friedel–Crafts arylation protocol, **11d** was converted to **12d** in 86% yield. Desilylation of **12d** with TBAF quantitatively afforded **13d**, a trimethyl-protected form of selaginpulvilin C. Finally,

Scheme 3. Total Synthesis of Selaginpulvilin D



Scheme 4. Total Synthesis of Selaginpulvilin C



global cleavage of the methyl ethers with methylmagnesium iodide resulted in the formation of selaginpulvilin C in 69% yield,[13] which constitutes a short total synthesis of the natural product.

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In summary, we have accomplished total syntheses of selaginpulvilins C and D. The construction of the core fluorene moiety of these natural products relies on a strategy that involves in situ formation of an aryne intermediate via the hexadehydro Diels–Alder reaction (HDDAR) followed by formal hydrogenation of the aryne moiety. The required tetrayne substrates for HDDAR were prepared efficiently via repetitive use of alkyne-coupling reactions starting from readily available building blocks. We are pursuing the synthesis of selaginpulvilins A and B and other structurally diverse analogues for structure–activity relationship studies on the basis of HDDAR-based approaches, which will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03241.

Detailed experimental procedures, characterization data, ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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