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ARTICLE

Formal Total Synthesis of Selaginpulvilin D

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An efficient and mild synthetic strategy for the total synthesis of selaginpulvilins D has been reported. A highly chemoselective enyne-alkyne dehydro Diels-Alder reaction has been employed for the construction of the tricyclic fluorene framework present in the natural product selaginpulvilin D. Improved overall yield (10.5%) has been achieved for selaginpulvilin D, starting from commercially available *m*-anisaldehyde in 9 linear, operationally simple synthetic transformations.

Introduction

Fluorene derivatives are a group of structurally rigid compounds featuring a 6-5-6 carbocyclic system. They are considered as privileged structures in pharmaceutical industry also used in optical and electronic materials.[1] Though numerous synthetic fluorene derivatives were reported in the literature, the natural fluorenes are very rare. So far, only about twelve natural fluorene derivatives (includes nine simple fluorenones, one dihydroazafluoranthene alkaloid, and two benzofluorenones) have been reported from plant resources.[2] Selaginella pulvinata (*Selaginellaceae*), a species in the Chinese Pharmacopoeia, has been well used in traditional Chinese medicines for the treatment of dysmenorrhea, asthma, and traumatic injury. During the phytochemical investigation on *S. pulvinata* by the research group of Yin and co-workers, they observed that a fraction of the ethanol extract showed significant phosphodiesterase-4 (PDE4) inhibitory activity. Subsequent chemical investigation led to the isolation of four new phenolic natural products selaginpulvilins A–D **1-4** with an unprecedented 9,9-diphenyl-1-(phenylethynyl)-9*H*-fluorene skeleton **5**, together with four known selaginellin natural products (Figure 1).[3a] Compounds **1-4** found to be the most potent natural PDE4 inhibitors discovered to date, by showing remarkable inhibitory activities against PDE4 with IC_{50} values in the range of 0.11–5.13 µM. In particular selaginpulvilin B **2**, the most active compound showed an IC_{50} of 0.11 µM, being 5-fold stronger than the b-positive control. Further, phytochemical studies on EtOAc extract of *S. pulvinata* lead to the isolation of six new analogues selaginpulvilins E-J **6-11**.[3b] Recently, two more members of this family of natural products, selaginpulvilin K and L **12** and **13** have also been isolated.[3c]

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It is the unique skeleton of selaginpulvilins A–L, which may renders potent activity and makes them rare and promising lead structures for the development of natural PDE4 inhibitors. The interesting bioactivities associated with their novel and unique structures made these natural products attractive synthetic targets for the total synthesis. Developing short, efficient and practical synthetic approaches for these molecules will provide an opportunity to study and explore their new biological properties. Recently there are three reports appeared on the total synthesis of this family of natural products.[4] Herein we report an efficient approach for the formal total synthesis of selaginpulvilin D **4** employing the enyne-alkyne dehydro Diels-Alder cyclization as the key step.

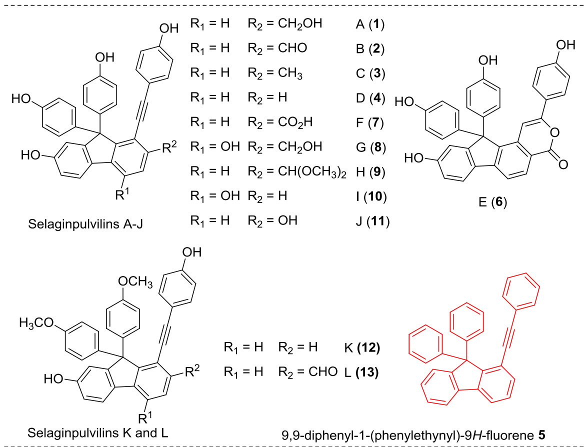
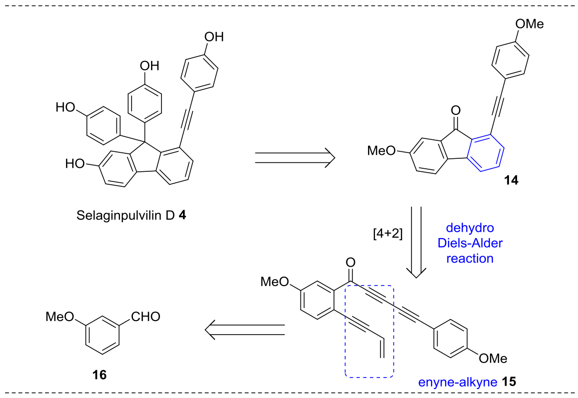


Figure 1 Structures of selaginpulvilins A-L

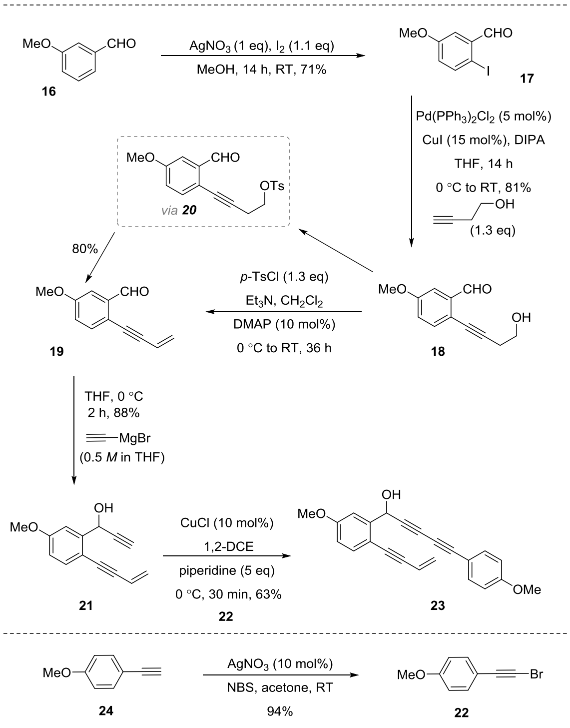
According to our retrosynthetic analysis (Scheme 1), the selaginpulvilin D **4** can be generated from the corresponding fluorenone **14** *via* the creation of tetraarylmethane system from the diarylcarbonyl system. The fluorenone **14** can easily be obtained from the enyne-alkyne **15** *via* a chemoselective dehydro Diels-Alder reaction.[5] The synthesis of **15** was envisioned from commercially available 3-methoxybenzaldehyde **16** employing simple synthetic transformations.



Scheme 1 Designed retrosynthetic plan for selaginpulvilin D

Results and Discussion

To begin with, we aimed to synthesize the key precursor for the Diels-Alder reaction (Scheme 2). Accordingly, treatment of *m*-anisaldehyde **16** with $AgNO_3$ and I_2 in methanol at RT, gave the 2-iodo-5-methoxybenzaldehyde **17** in 71% yield.[6] The Sonogashira cross coupling[7] of **17** with 1-butynol in presence of $PdCl_2(PPh_3)_2$ and CuI in THF and diisopropylamine (DIPA) generated the coupled product **18** in excellent yield (81%) after 14 h at RT. Reaction of hydroxy-aldehyde **18** with *p*-TsCl and triethylamine (TEA) in presence of catalytic amount of DMAP at RT for 36 h, directly provided the enyne moiety **19** *via* the corresponding tosylate **20** intermediate.



Scheme 2 Preparation of the enyne-alkyne precursor for DDA reaction. THF: tetrahydrofuran; DIPA: diisopropylamine; DMAP: 4-(dimethylamino)pyridine; 1,2-DCE: 1,2-dichloroethane; NBS: *N*-bromosuccinimide

To create the required diyne moiety on the aldehyde part of the **19**, we employed a two step strategy. Addition of ethynylmagnesium bromide to the aldehyde **19** at 0 °C in THF resulted in the formation of a secondary propargylic alcohol **21** in 88% yield. The cross coupling of the terminal alkyne in the propargylic alcohol **21** with the alkynylbromide **22** under the modified Cadiot-Chakowidcz coupling conditions[8] i.e., in presence of CuCl and piperidine (5 equiv.), in 1,2-dichloroethane (1,2-DCE) gave the enyne-diynol **23** in 63% yield. The alkynylbromide **22** was efficiently prepared from commercially available 4-methoxyphenylacetylene **24** following a known procedure.[9]

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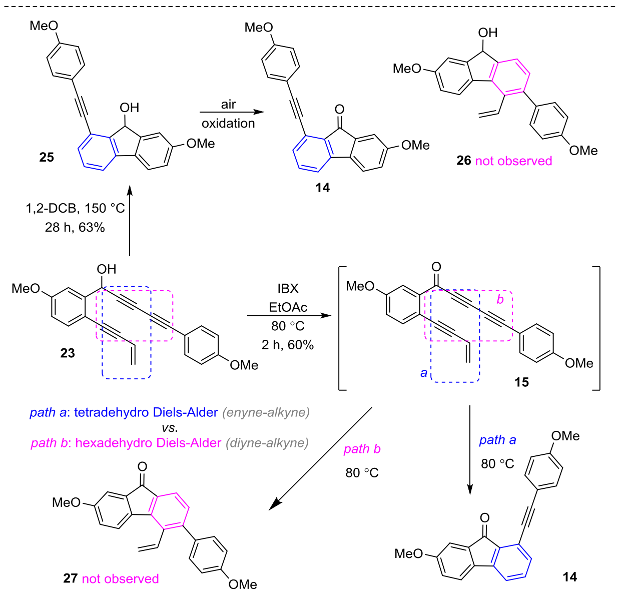
Keeping the required enyne-diyne **23** in hand, next, in order to test the feasibility of the designed DDA reaction, we subjected **23** to thermal heating conditions. Heating a solution of **23** in 1,2-DCB at 150 °C for 28 h, smoothly underwent the expected cyclisation and provided to our delight directly the fluorenone derivative **14** in 63% yield. Formation of **14** can be explained *via* the highly chemoselective dehydro Diels-Alder reaction, followed by the air oxidation of the bis-benzylic alcohol **25** under reaction conditions. Alternatively, we also thought that converting the alcohol **23** to the corresponding ketone **15** might activate the substrate towards the DDA reaction and may lead to the efficient synthesis of fluorene derivative **14**. Accordingly, when the diynol **23** was treated with IBX[10] in EtOAc at 80 °C directly resulted in the formation of the cyclised fluorenone derivative **14** *via* a highly chemoselective DDA reaction between an enyne and alkynone of the in situ generated ketone **15** (Scheme 3).



Scheme 3 Efficient generation of fluorene framework of selaginpulvilin D *via* a highly chemoselective enyne-alkyne dehydro Diels-Alder reaction. 1,2-DCB: 1,2-dichlorobenzene

It is noteworthy to mention here that, both the alcohol **23** and ketone **15** can in principle undergo two different modes of Diels-Alder reactions, namely, either between an enyne and alkyne (tetradehydro Diels-Alder (TDDA) reaction) or between diyne and alkyne i.e., hexdehydro Diels-Alder (HDDA)

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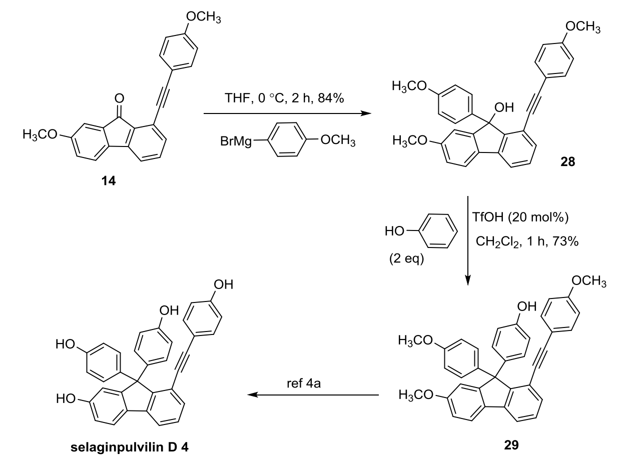
reaction.[11] Surprisingly, we could not detect any traces of the products **26** and **27**, which can be obtained from the **23** and **15** respectively, *via* the HDDA reaction. This clearly supports the fact that, activation energy[12] for the TDDA reaction is much lower than that required for the HDDA reaction and hence possibility for the chemoselective dehydro Diels-Alder reaction.



Scheme 4 Formal total synthesis of selaginpulvilin D

After synthesizing the tricyclic system **14** of the selaginpulvilin D **4**, next we focused to generate the required *tetra*-arylmethane present in the natural product. Accordingly addition of *p*-anisylmagnesium bromide to the tricyclic ketone **14** in THF at 0 °C generated the triarylmethanol **28** in excellent yield (84%). In continuation, treatment of the tertiary alcohol **28** with phenol in presence of TfOH (20 mol%) afforded the biarylated fluorene derivative **29**, i.e., trimethylated selaginpulvilin D, in good yield (73%) after 1 h *via* the aromatic electrophilic substitution reaction. Conversion of **29** to the natural product selaginpulvilin D **4** *via* demethylation reaction has already been reported.[4a] Hence, this overall synthetic scheme for the generation of the **29** from *m*-anisaldehyde **16** constitutes an efficient formal total synthesis of selaginpulvilin D **4**. In the literature, both the reported total syntheses[4a,b] for this natural product **4** have the overall yields of 4.4% and 17%. Our strategy involves nine mild, linear steps and provides the access to the selaginpulvilin D **4** with an overall yield of 7.5% (or 10.5% from iodo-anisaldehyde **17**).

Conclusions

In conclusion we have developed a linear, mild and efficient synthetic scheme for the formal total synthesis of selaginpulvilin D, with an overall yield of 10.5%. We employed the dehydro Diels-Alder reaction of an enyne-alkyne unit for the generation of the tricyclic fluorene derivative in a highly chemoselective manner. Further extension of this strategy for other members of this selaginpulvilin family of natural products is in progress in our laboratory.

Acknowledgements

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Experimental Section

Reactions were monitored by thin-layer chromatography (TLC) carried out on Merck silica plates using UV light and anisaldehyde or potassium permanganate stains for visualization. Column chromatography was performed on silica gel (60–120 mesh) using hexanes and ethyl acetate as eluents. NMR data were recorded on 400 and 500 MHz spectrometers. ^{13}C and ^{1}H chemical shifts in NMR spectra were referenced relative to signals of $CDCl_3$ (δ 7.263 ppm for ^{1}H and 77.16 ppm for ^{13}C). Chemical shifts δ and coupling constants J are given in ppm (parts per million) and Hz (hertz), respectively. Multiplicities were given as: s (singlet); d (doublet); t (triplet); q (quartet); dd (doublets of doublet) or m (multiplets). HRMS were recorded by electron spray ionization (ESI) method on a Q-TOF Micro with lock spray source. Known compounds data have been compared with the reported data, and references were given appropriately. Characterization data for new compounds are given below. ^{1}H and ^{13}C (proton decoupled) NMR spectra for all new compounds are given in the ESI Reagents were purchased from chemical companies.

For full details of all experiments, spectroscopic data and ^{1}H & ^{13}C-NMR data for all new compounds see the Supporting Information

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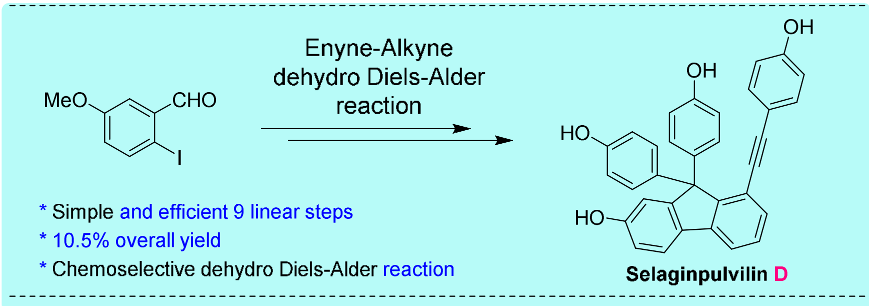

TOC text:

An efficient formal total synthesis of selaginpulvilin D has been achieved, employing a chemoselective dehydro Diels-Alder reaction as the key step.