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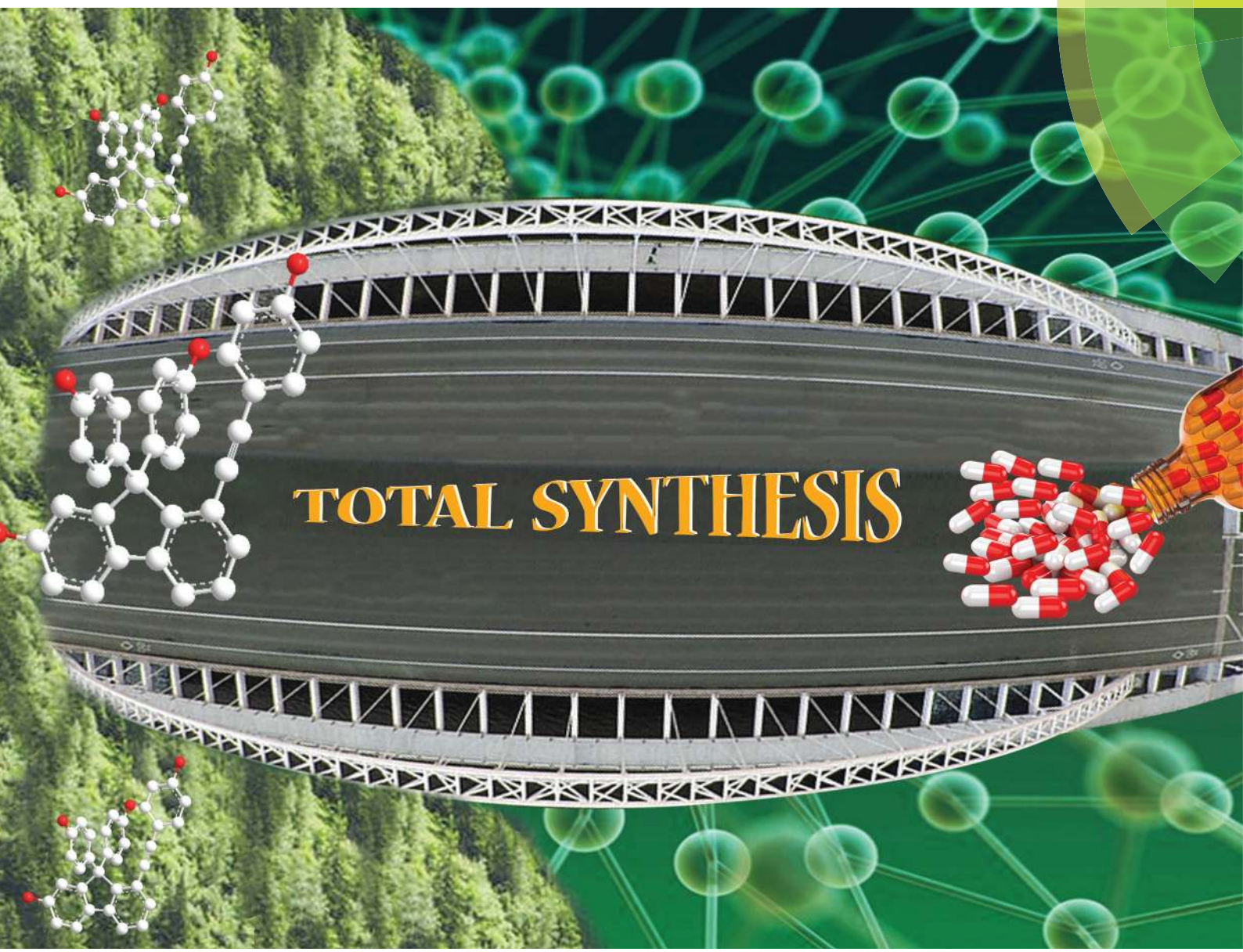

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Formal total synthesis of selaginpulvilin D†

Bhavani Shankar Chinta and Beeraiah Baire *

An efficient and mild synthetic strategy for the total synthesis of selaginpulvilin 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. An 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 important structures in the pharmaceutical industry and are also used in optical and electronic materials.[1] Though numerous synthetic fluorene derivatives have been reported in the literature, natural fluorenes are very rare. So far, only about twelve natural fluorene derivatives (including 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 (Fig. 1).[3a] Compounds **1–4** have been 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} value of 0.11 μM, being 5-fold stronger than the b-positive control. Further, phytochemical studies on the EtOAc extract of *S. pulvinata* led 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]

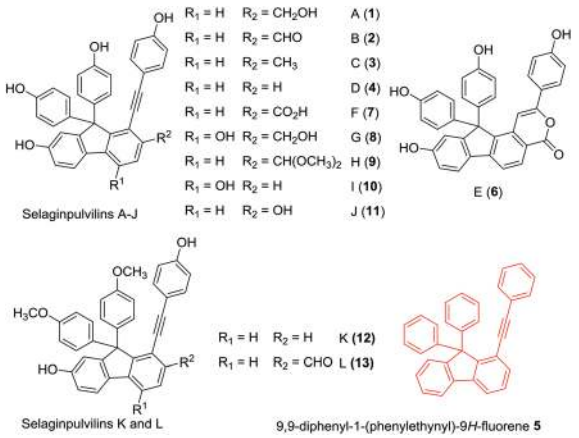

Fig. 1 Structures of selaginpulvilins A–L.

It is the unique skeleton of selaginpulvilins A–L, which may render potent activity and make 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 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 have been three reports 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.

According to our retrosynthetic analysis (Scheme 1), the selaginpulvilin D **4** can be generated from the corresponding fluorenone **14** *via* the creation of a tetraarylmethane system from the diarylcarbonyl system. The fluorenone **14** can easily be obtained from the enyne–alkyne **15** *via* a chemoselective

Department of Chemistry, Institute of Technology Madras, Chennai-600036, India. E-mail: beeru@iitm.ac.in

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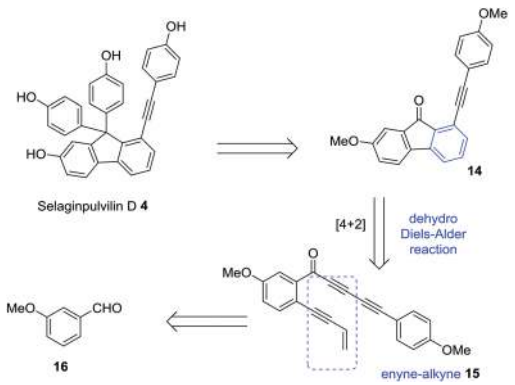
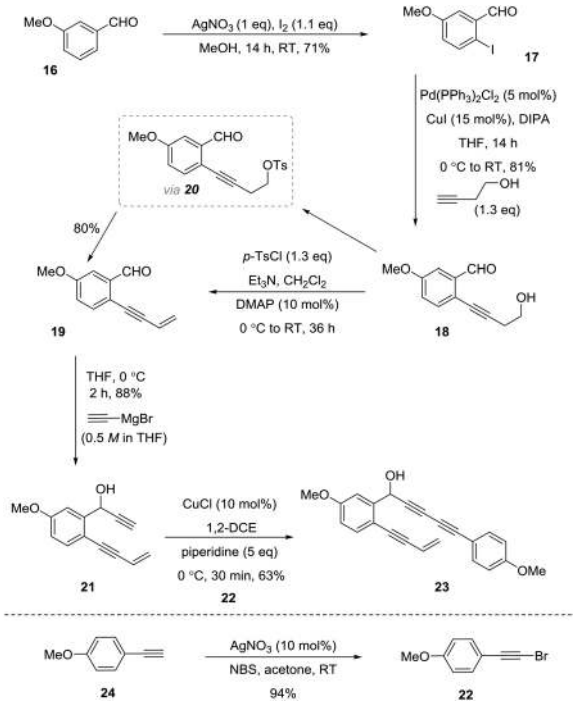


Scheme 1 Designed retrosynthetic plan for selaginpulvilin D.

dehydro Diels–Alder reaction.[5] The synthesis of **15** was envisioned from commercially available 3-methoxybenzaldehyde **16** employing simple synthetic transformations.

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 the presence of $PdCl_2(PPh_3)_2$ and CuI in THF and diisopropylamine (DIPA) generated the coupled product **18** in an excellent yield (81%) after 14 h at RT. The reaction of hydroxy-aldehyde **18** with *p*-TsCl and triethylamine (TEA) in the presence of a catalytic amount of DMAP at RT for 36 h directly provided the enyne moiety **19** *via* the corresponding tosylate **20** intermediate.



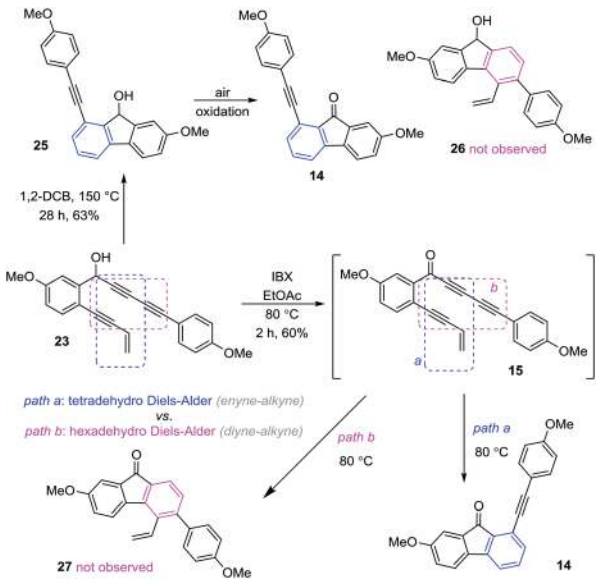
Scheme 2 Preparation of the enyne–alkyne precursor for the DDA reaction. THF: tetrahydrofuran; DIPA: diisopropylamine; DMAP: 4-(dimethylamino)pyridine; 1,2-DCE: 1,2-dichloroethane; NBS: *N*-bromosuccinimide.

To create the required diyne moiety on the aldehyde part of **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 the 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]

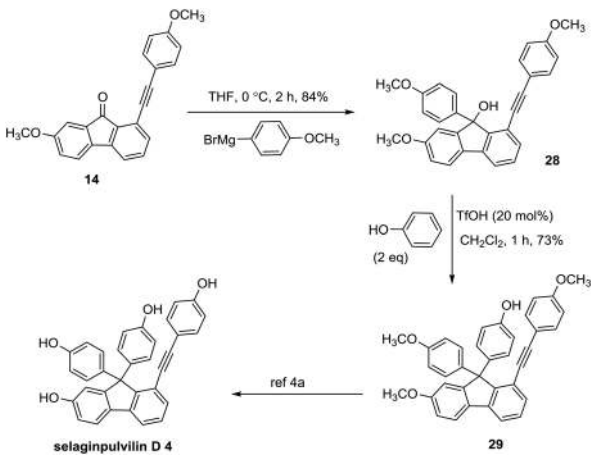
With the required enyne–diyne **23** in hand, next, in order to test the feasibility of the designed DDA reaction, we subjected **23** to thermal heating conditions. Heating a solution of **23** in 1,2-DCB at 150 °C for 28 h led to the expected cyclisation proceeding smoothly and to our delight directly provided the fluorenone derivative **14** in 63% yield. The formation of **14** can be explained *via* the highly chemoselective dehydro Diels–Alder reaction, followed by air oxidation of the bis-benzylic alcohol **25** under the 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, treatment of the diynol **23** 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).

It is worthy of 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 a diyne and alkyne *i.e.*, the hexadehydro Diels–Alder (HDDA) reaction.[11] Surprisingly, we could not detect any traces of the products **26** and **27**, which can be obtained from **23** and **15** respectively, *via* the HDDA reaction. This clearly supports the fact that the 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.

After synthesizing the tricyclic system **14** of the selaginpulvilin D **4**, we focused on generating the required *tetra*-arylmethane present in the natural product (Scheme 4). 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 the 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



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



Scheme 4 Formal total synthesis of selaginpulvilin D.

29 to the natural product selaginpulvilin D **4** *via* the demethylation reaction has already been reported.[4a] Hence, this overall synthetic scheme for the generation of **29** from *m*-anisaldehyde **16** constitutes an efficient formal total synthesis of selaginpulvilin D **4**. According to the literature, both the reported total syntheses[4a,b] for this natural product **4** gave the overall yields of 4.4% and 17%. Our strategy involves nine mild, linear steps and provides 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.

Experimental section

The 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 the 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 spectra were recorded by the electron spray ionization (ESI) method on a Q-TOF Micro with a lock spray source. The data of the known compounds have been compared with the reported data, and references were given appropriately. Characterization data for new compounds are given below. The ^{1}H and ^{13}C (proton decoupled) NMR spectra for all new compounds are given in the ESI.† The 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 ESI.†

Acknowledgements

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