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ARTICLE

Total Synthesis of Selaginpulvilins A and C

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An efficient formal total synthesis of selaginpulvilin family of natural products selaginpulvilin A and C has been successfully achieved. The tetradehydro Diels-Alder (TDDA) reaction between an enyne and alkyne has been utilized for the creation of necessary fluorene skeleton. Attempts for the conversion of selaginpulvilin A to selaginpulvilin B, F and H were unsuccessful.

Introduction

Selaginella pulvinata (*Selaginellaceae*) is a species in the Chinese Pharmacopeia, which has been well utilized in traditional Chinese medicines for the treatment of dysmenorrhea, asthma, and traumatic injury. The phytochemical investigation on *S. pulvinata* by the research group of Yin and co-workers, led to the isolation of four new natural products selaginpulvilins A–D **1-4** with an unprecedented 9,9-diphenyl-1-(phenylethynyl)-9*H*-fluorene skeleton along with several known natural products (Figure 1).[1a] These compounds **1-4** exhibit the remarkable phosphodiesterase-4 (PDE4) inhibitory activity with IC_{50} values in the range of 0.11−5.13 μM. They found to be the most potent natural PDE4 inhibitors discovered to date. Further, phytochemical studies on EtOAc extract of *S. pulvinata* resulted in the isolation of eight new analogous selaginpulvilins E-L **5-12**.[1b-c]

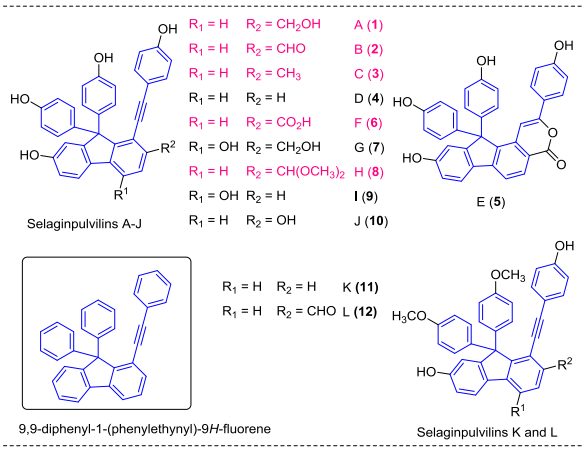
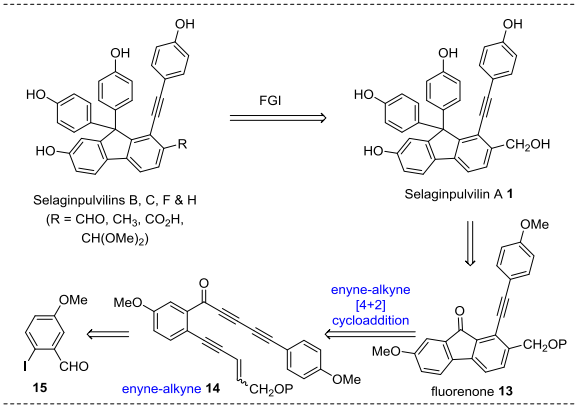


Figure 1 Selaginpulvilin natural products

The unique fluorene[2,3] skeleton associated with important bioactivities, makes selaginpulvilins interesting target molecules for the synthetic organic chemists. So far there are four reports appeared on the total synthesis of this family of natural products.[4] Recently we also developed an efficient approach for the formal total synthesis of selaginpulvilin D **4** employing the enyne-alkyne dehydro Diels-Alder cyclization as the key step.[4d] In continuation, we aimed to extend this strategy for the total synthesis of other members of selaginpulvilin family of natural products. In this context, we envisioned that, the selaginpulvilin A **1** can be served as a suitable intermediate for the total synthesis of the natural products selaginpulvilins B, C, F and H.

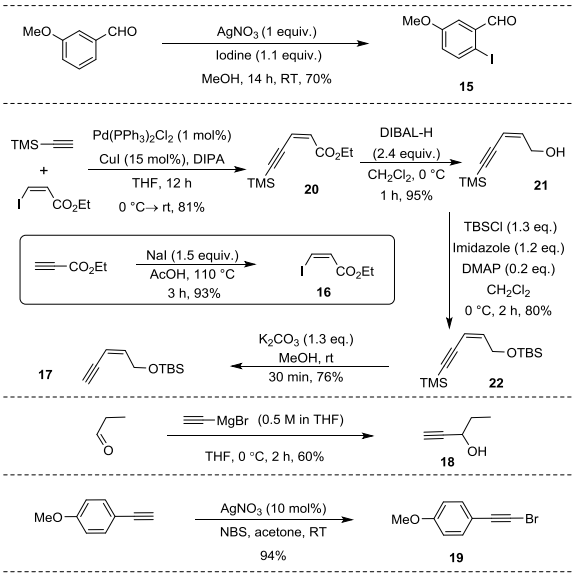


Scheme 1 Retrosynthetic plan for selaginpulvilins A-C, F and H

According to our retrosynthetic analysis (scheme 1), selaginpulvilins B (CHO) **2**, F (CO_2H) **6**, H ($CH(OMe)_2$ **8**, and C (CH_3) **3** could be synthesized from the selaginpulvilin A **1** *via* various functional group interconversions (FGI) of hydroxymethyl group present in it, such as oxidation to aldehyde and acid, dimethylacetal formation from aldehyde and deoxygenation to methyl group respectively. The selaginpulvilin A **1** can be achieved from the fluorenone derivative **13** via diarylation protocol. This **13** can be generated from enyne-alkyne **14** *via* the tetradehydro Diels-Alder (TDDA) reaction.[5] The enyne-alkyne **14** can be synthesized from 2-iodo-5-methoxybenzaldehyde **15**.

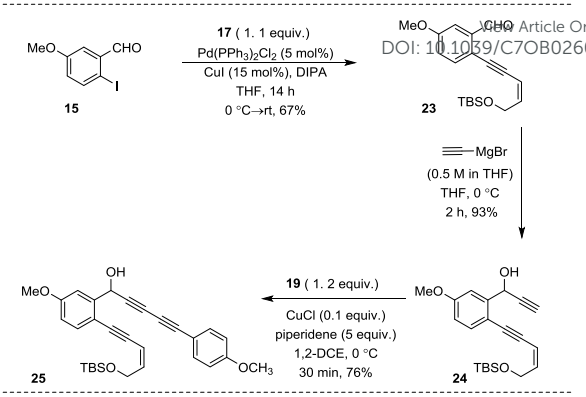
Results and Discussion

To begin with, we synthesized several key building blocks **15-19**, which will be utilized during the designed total synthesis (scheme 2) employing the literature procedures. Accordingly, reaction of the *m*-anisaldehyde with $AgNO_3$ and I_2 in methanol at RT, gave the 2-iodo-5-methoxybenzaldehyde **15** in 70% yield.[6] Next, the Sonogashira cross coupling[7] of TMS-acetylene with ethyl *Z*-2-iodoacrylate **16** in presence of $PdCl_2(PPh_3)_2$ and CuI in THF and diisopropylamine (DIPA) generated the coupled product **20**.[8] Further reduction of the ester with DiBAL-H gave the primary alcohol **21**.[8] Protection of this primary alcohol employing TBS-Cl and imidazole followed by the deprotection of trimethylsilyl (TMS) group present in **22** with K_2CO_3-MeOH at RT afforded the corresponding ynenol-TBS-ether **17**. The *Z*-2-iodoacrylate **16** was synthesized from the reaction of methyl propiolate with NaI in AcOH under refluxing conditions.[9] The pentyn-3-ol **18** was prepared from the reaction between ethynyl Grignard and propanaldehyde at 0 °C in THF.[10] Another building block, the alkynylbromide **19** was efficiently prepared from commercially available 4-methoxyphenylacetylene following a known procedure.[11]



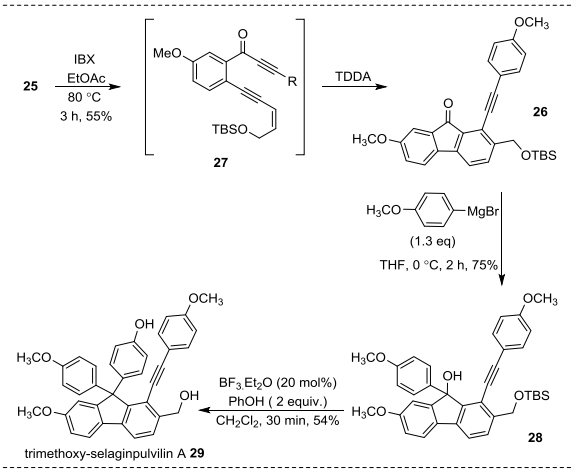
Scheme 2 Preparation of the key building blocks. THF: tetrahydrofuran; NBS: N-bromosuccinimide.

After synthesizing the required building blocks, we next began our synthesis of selaginpulvilin A **1** (scheme 3). The Sonogashira cross coupling of **15** with alkynyl-TBS-ether **17** generated the coupled aldehyde **23** in 67% yield. Ethynylmagnesium bromide addition to the aldehyde **23**, followed by the coupling of the resultant secondary propargylic alcohol **24** with the alkynylbromide **19** in presence of CuCl (10 mol%) and piperidine (5 equiv.), in 1,2-dichloroethane (1,2-DCE) gave the enyne-diynol **25** in 65% yield (for two steps).[12]



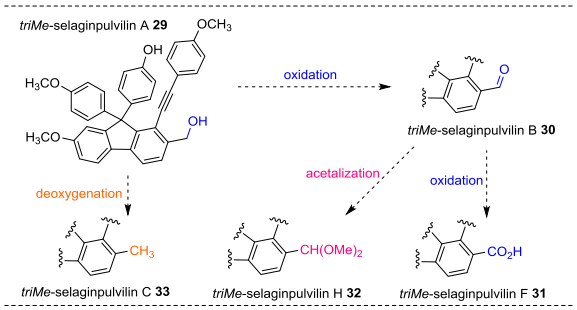
Scheme 3 Synthesis of the enyne-alkyne precursor for TDDA. DIPA: diisopropylamine; 1,2-DCE: 1,2-dichloroethane.

Subsequently, the enyne-diynol **25** was treated with IBX[13] in EtOAc at 80 °C. After 3 h, the reaction gave directly the fluorene derivative **26** via the oxidation followed by the TDDA cyclization reaction of the resultant ketone **27** (scheme 4). Next the tetra aryl chiral carbon was generated employing a two step protocol. The *p*-anisylmagnesium bromide addition to **26** gave the *tert*-alcohol **28**. A Friedel-Crafts alkylation with the alcohol **28** and phenol in presence of $BF_3.Et_2O$ resulted directly the formation of the trimethoxy-selaginpulvilin A **29** through the TBS-deprotection. This synthetic scheme constitutes the formal total synthesis of selaginpulvilin A **1** as the conversion of **29** to **1** is already known in the literature.[4b]



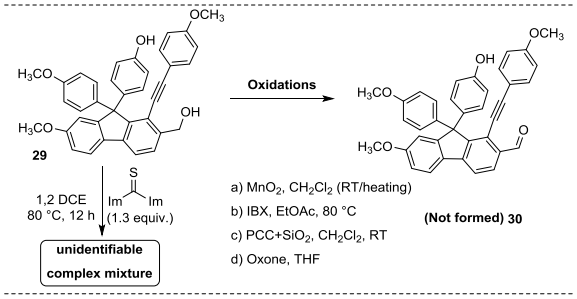
Scheme 4 Formal total synthesis of selaginpulvilin A **1**

In continuation, we envisioned an opportunity for the total synthesis of other members of this family of natural products from the trimethoxy-selaginpulvilin A **29** (scheme 5). A controlled oxidation of the benzylic alcohol present in **29** can provide the aldehyde **30**, which is the trimethoxy-selaginpulvilin B. Further oxidation of this aldehyde **30** affords the acid i.e., trimethoxy-selaginpulvilin F **31**, whereas the dimethylacetal formation gives the trimethoxy-selaginpulvilin H **32**. In another direction deoxygenation of the hydroxyl group present in trimethoxy-selaginpulvilin A **29** should generate the trimethoxy-selaginpulvilin C **33**.



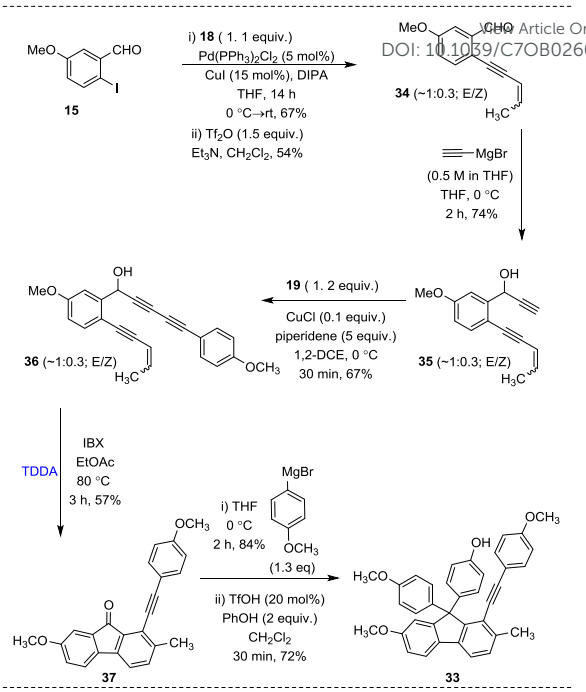
Scheme 5 Design for the synthesis of selaginpulvilins B, C, F and H

But to our disappointment, there was no oxidation of hydroxyl group present in **29** occurred (scheme 6). Various conditions and reagents such as MnO_2, IBX, PCC, oxone etc. failed to give any traces of either the aldehyde or acid. In all cases a slow decomposition of the starting alcohol **29** was observed. Further we attempted for the selective mono-deoxygenation of **29**, via a xanthate formation. But there was no clean reaction under standard xanthate formation conditions.



Scheme 6 Attempts for the oxidation and deoxygenation of trimethoxy-selaginpulvilin A **29**

As the oxidation and deoxygenation reactions on trimethoxy-selaginpulvilin A **29** found to be not feasible, subsequently, we envisioned and developed the TDDA based approach for the total synthesis of selaginpulvilin C **3** starting from the iodo-aldehyde **15** (scheme 8). Accordingly, the Sonogashira coupling with the pentyn-3-ol **18** followed by dehydration of the resultant coupled alcohol using Tf_2O and triethylamine gave the enyne-aldehyde **34** as a ~(1:0.3) mixture of E/Z isomers. Addition of ethynylmagnesium bromide to the aldehyde **34** and CuCl catalyzed Cadiot-Chodkiewicz coupling of the resultant secondary propargylic alcohol **35** [a ~ (1:0.3) mixture of E/Z isomers] with the alkynylbromide **19** gave the required enyne-alkynol **36** [a ~ (1:0.3) mixture of E/Z isomers] in 50% overall yield for two steps. Oxidation of the alcohol **36** with IBX at 80 °C gave the fluorenone derivative **37** (57% yield), after 3 h. Further, a two-step strategy involving *p*-anisylmagnesium bromide addition to the fluorenone **37** followed by the Friedel-Crafts alkylation of phenol with the resultant *tert*-alcohol in presence of TfOH gave the target molecule trimethoxy-selaginpulvilin C **33** in 60% yield (two steps). Conversion of **33** to selaginpulvilin C **3** has already been reported in the literature;[4a] hence this synthetic scheme represents the formal total synthesis of this natural product.



Scheme 7 Formal total synthesis of selaginpulvilin C **3**

Conclusions

In conclusion, the formal total synthesis of two of the selaginpulvilin family natural products sealiginpulvilin A and C has been achieved by employing an efficient strategy. The chemo selective tetradehydro Diels-Alder reaction has been employed as the key transformation to build the fluorenone framework. Attempts for the conversion of selaginpulvilin A to selaginpulvilin B, F and H were unsuccessful.

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

Notes and references

1 (a) X. Liu, H. -B. Luo, Y. -Y. Huang, J.-M. Bao, G.-H. Tang, Y.-Y. Chen, J. Wang and S. Yin, *Org. Lett.* **2014**, *16*, 282; (b) J.-S. Zhang, X. Liu, J. Weng, Y. -Q. Guo, Q. -J. Li, A. Ahmed, G. -H. Tang and S. Yin, *Org. Chem. Front.*, **2017**,*4*, 170; (c) Y. Huang, X. Liu, D. Wu, G. Tang, Z. Lai, X. Zheng, Y. Sheng, H. -B. Luo, *Biochemical Pharmacology,* **2017**, ASAP. doi: http:// dx.doi.org/10.1016/j.bcp.2017.01.016.

2 (a) L. C. Okell, M. Cairns, J. T. Griffin, N. M. Ferguson, J. Tarning, G. Jagoe, P. Hugo, M. Baker, U. D'Alessandro, T. Bousema, D. Ubben and A. C. Ghani, *Nat. Commun.*, **2014,** *5,* 6606; (b) F. Gualtieri, E. Teodori, C. Bellucci, E. Pesce and G. Piacenza, *J. Med. Chem.*, **1985**, *28*, 1621; (c) J. Z. Song, F. T. Lv, G. M. Yang, L. B. Liu, Q. Yang and S. Wang, *Chem. Commun.*, **2012**, *48*, 7465; (d) P. I. Shih, C. L. Chiang, A. K. Dixit, C. K. Chen, M. C. Yuan, R. Y. Lee, C. T. Chen, E. W. G. Diau and C. F. Shu, *Org. Lett.*, **2006**, *8*, 2799; (e) T. Oyamada, C. H. Chang, T. C. Chao, F. C. Fang, C. C. Wu, K. T. Wong, H. Sasabe and C. Adachi, *J. Phys. Chem. C,* **2007**, *111*, 108.

3 Y. B. Shi and S. H. Gao, *Tetrahedron* **2016**, *72*, 1717.

4 (a) R. Karmakar and D. Lee, *Org. Lett.,* **2016**, *18*, 6105; (b) M. J. Sowden and M. S. Sherburn, *Org. Lett.,* **2017**, *19*, 636; (c) J.-S. Zhang, X. Liu, J. Weng, Y.-Q. Guo, Q.-J. Li, A. Ahmed, G.-H. Tang and S. Yin, *Org. Chem. Front.,* **2017**, *4*, 170; (d) B. S. Chinta and B. Baire, *Org. Biomol. Chem.,* **2017***, 15*, 5908.

5 (a) A. Michael and J. E. Bucher, *Chem. Zentrblt*., **1898**, 731; (b) O. Diels and K. Alder, *Justus Liebigs Ann. Chem.* **1928**, *460*, 98; (c) P. Wessig and G. Müller, *Chem. Rev*. **2008**, *108*, 2051; (d) R. L. Danheiser, A. E. Gould, R. F. Pradilla and A. L. Helgason, *J. Org. Chem.* **1994**, *59*, 5514; (e) J. R. Dunetz and R. L. Danheiser, *J. Am. Chem. Soc.* **2005**, *127*, 5776; (f) M. E. Hayes, H. Shinokubo and R. L. Danheiser, *Org. Lett.,* **2005**, *7*, 3917; g) M. S. B. Wills and R. L. Danheiser, *J. Am. Chem. Soc.* **1998,** *120,* 9378; (h) B. S. Chinta, A. Siraswar and B. Baire, *Tetrahedron,* **2017***, 73,* 4178; (i) B. S. Chinta and B. Baire, *Eur. J. Org. Chem.,* **2017***,* 3381; (j) B. S. Chinta and B. Baire, *Eur. J. Org. Chem.,* **2017***,* 3381.

6 W. Ma, J. Fang, J. Ren and Z. Wang, *Org. Lett.*, **2015**, *17*, 4180.

7 (a) K. Sonogashira, *J. Organomet. Chem.* **2002**, *653*, 46; (b) R. Chinchilla and C.́ Najera, *Chem. Soc. Rev.* **2011**, *40*, 5084.

8 S. Arai, Y. Koike, H. Hada and A. Nishida., *J. Am. Chem. Soc.,* **2010**, *132*, 4522.

9 D. Beruben, I. Marek, J. F. Normant and N. Platzer., *J. Org. Chem.,* **1995**, *60*, 2488.

10 Z. Lu and Shengming Ma., *J. Org. Chem.,* **2006**, *71*, 2655.

11 (a) T. Nishikawa, S. Shibuya and S. Hosokawa, *Synlett*, **1994,** *7*, 485; (b) K. S. Youngchan, B. Ramesh, S. Dateer and S. Chang, *Org. Lett.*, **2017**, *19*, 190.

12 (a) W. Chodkiewicz and P. Cadiot, *C. R. Hebd. Seances Acad. Sci.,* **1955**, *241*, 1055; (b) W. Chodkiewicz, *Ann. Chim.* **1957**, *2*, 819; (c) K. Sonogashira, In *Comprehensive Organic Synthesis*; B. M. Trost and I. Fleming, Eds.; Pergamon Press: Oxford, UK, **1991**; Vol. *3*, pp 551-561; (d) K. S. Sindhu, A. P. Thankachan, P. S. Sajitha and G. Anilkumar, *Org. Biomol. Chem.,* **2015**, *13*, 6891.; (e) B. S. Chinta and B. Baire, B. *RSC Advances,* **2016***, 6*, 54449; (f) B. S. Chinta and B. Baire, *J. Org. Chem.,* **2015**, *80*, 10208.

13 M. Frigerio, M. Santagostino and S. Sputore, *J. Org. Chem.* **1999**, *64*, 4537.

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Total Synthesis of Selaginpulvilins A and C

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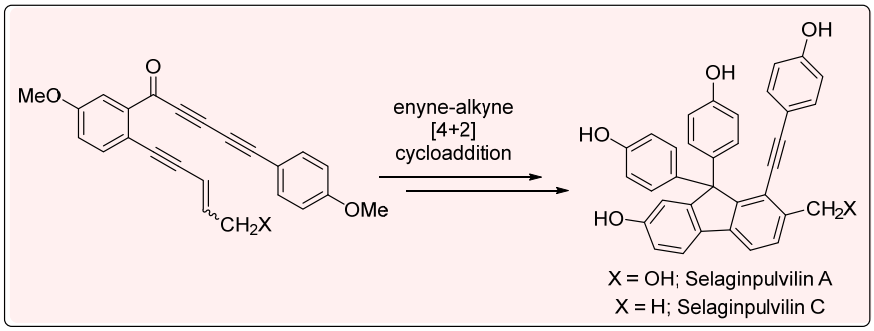

TOC text:

An efficient strategy for the formal total synthesis of selaginpulvilins A and C has been reported. This approach involves 6 and 7 linear synthetic operations associated with 10% and 7% overall yield respectively for selaginpulvilins A and C.