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Catalytic Cyclotrimerization Pathway for Synthesis of Selaginpulvilins C and D: Scope and Limitations

Lukas Rycek, Miguel Mateus,‡ Nela Beytlerová,‡ and Martin Kotora*

Cite This: https://dx.doi.org/10.1021/acs.orglett.1c00519 Read Online

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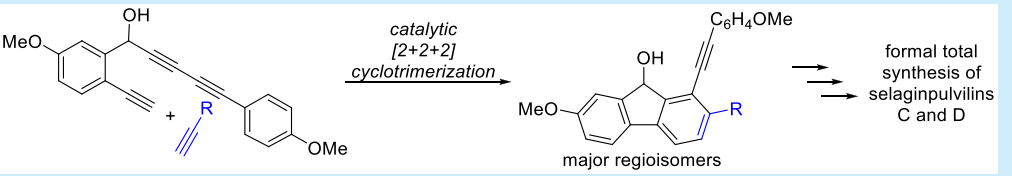


ABSTRACT: A facile and unified approach to the main selaginpulvilin's framework was achieved by catalytic [2 + 2 + 2]-cyclotrimerization of a triyne with monosubtituted alkynes. The reaction proceeded with high "*ortho*" selectivity by using Wilkinson's catalyst ($RhCl(PPh_3)_3$) under ambient conditions with reasonable yields. The scope of the reaction with respect to the alkyne as well as the catalytic system was evaluated. The formal total modular syntheses of selaginpulvilin C and D were accomplished by transformation of the cyclotrimerization's products.

Natural compounds possess a diverse spectrum of intriguing polycyclic carbon skeletons. Some of them seem to be somewhat unexpected and surprising. One such class of compounds are substances containing the fluorene scaffold. The presence of methylated fluorenes (namely 1,2,3,4-tetraalkylated fluorenes) has been confirmed in nature—they were detected in aromatic fractions of Athabasca oil sand bitumens.[1] However, until recently, there have not been any reports on the existence of more complex compounds possessing the fluorene skeleton (excluding those with the fluorenone moiety[2]). In 2014, Yin and co-workers reported isolation and characterization of four selaginpulvilins A–D (**1**) (Figure 1), new phenols with an unprecedented 9,9-diphenyl-1-(phenylethynyl)-9*H*-fluorene skeleton, from a plant used in traditional Chinese medicine *Selaginella pulvinata*.[3] Interestingly, selaginpulvilins A–D showed high inhibitory activity against PDE4D2 with IC_{50} values in the range 0.11–0.26 μM. The high activity values might explain the anti-inflammatory activity of the previously mentioned usage of *Selaginella pulvinata* plants. Later, the same plant's content reinvestigation led to the identification and isolation of other selaginpulvilins (E–J).[4,5] The densely substituted fluorene scaffold of selaginpulvilins has sparked great interest as a challenging target for synthesis. Since their isolation, total or formal syntheses of selaginpulvilins A–F based on various synthetic strategies have been disclosed. The reported synthetic strategy relied on (i) a hexadehydro Diels–Alder reaction of a tetrayne (selaginpulvilins A and C)[6] and (ii) a tetradehydro Diels–Alder reaction of an enyne–diyne (selaginpulvilins A, B and D),[7,8] and sequences comprising of cross-coupling reactions and an intramolecular S_EAr reaction.[9]

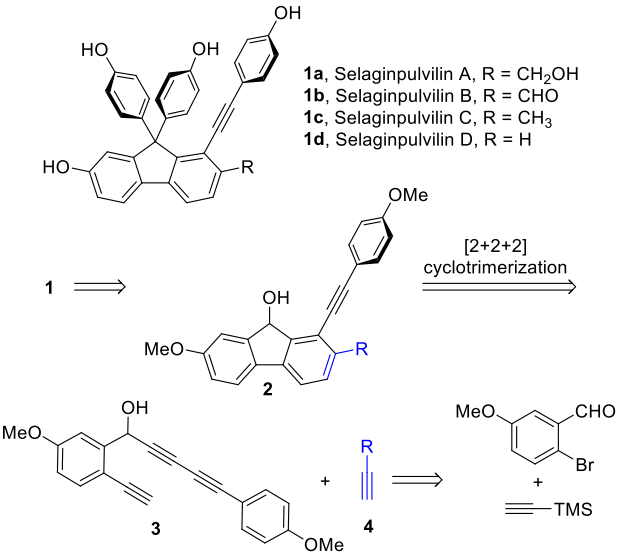


Figure 1. Selaginpulvilins A–D (**1a–1d**) and their retrosynthetic analysis.

Herein we would like to present a different synthetic approach toward selaginpulvilins based on a modular strategy. The approach relies on two key operations (Figure 1). The

Received: February 12, 2021

https://dx.doi.org/10.1021/acs.orglett.1c00519
Org. Lett. XXXX, XXX, XXX–XXX

first one is the crucial assembly of the aromatic ring on the right-hand side of the fluorenol's molecular scaffold **2** by using catalytic [2 + 2 + 2] cyclotrimerization of a substituted 1,3-diyne-yne **3** with alkynes **4**. The second one is synthesizing **3** from a 2-halo-5-methoxybenzaldehyde and trimethylsilylethyne by using standard methods of alkyne chemistry such as Sonogashira and Cadiot−Chodkiewicz couplings.

The reactivity of 1,3-diynes or their higher congeners in catalytic cycloaddition reactions has not been extensively studied, and only a few examples exist. For instance, homocyclotrimerization of 1,3-diynes to benzenes catalyzed by Pd,[10] Co,[11] Ni, and Rh[11c] complexes have been reported. Catalytic cocyclotrimerization (Co, Rh, Ir, and Ni complexes) of compounds having the 1,3-diyne moieties with alkynes and nitriles was explored as a route to various substituted biaryl or heterobiaryl compounds.[12−19]

On the other hand, cyclotrimerization of a 1,3-diyne-yne with alkynes to construct a single benzene ring is a relatively rare and unexplored field. Cramer's synthesis of fijiolide utilizing Ru-catalyzed cyclotrimerization of diyne-yne (connected by the B−O spacer) with an alkyne is the only example.[20] The lack of data in this field provides a sufficient impetus to explore the scope and synthetic applications of these reactions. In this respect, selaginpulvilins with their unique structure constitutes challenging synthetic objects to apply this methodology.

At the outset, we focused on the synthesis of the key intermediate **3**. It began with a Sonogashira coupling of 2-bromo-5-methoxybenzaldehyde and trimethylsilyl ethyne to furnish aldehyde **5** in 91% yield. Then NBS mediated bromination of 4-methoxyphenylethyne followed by Cadiot−Chodkiewicz coupling with trimethylsilyl ethyne provided TMS protected dialkyne (30% after two steps). Its desilylation furnished diyne **6** in 90% yield. Finally, alkynylation of aldehyde **5** with diyne **6** followed by desilylation gave rise to the desired triyne **3** in 58% yield after two steps (Scheme 1).

With a competent substrate in hand, we turned our attention to the key [2 + 2 + 2] cyclotrimerization step. Cyclotrimerization of **3** with propargyl alcohol (**4a**) catalyzed by Rh and Ru-complexes under various reaction conditions was chosen as the standard reaction (see Table S1 the Supporting Information (SI) for details). Mixtures of **2a** (*ortho*) and **2a′** (*meta*) regioisomers were obtained in all cases. The best selectivity for the desired *ortho* (**2a**:**2a′** = 9.5:1) and the moderate overall yield of 48% were obtained by using Wilkinson's catalysts in dichloroethane. Unlike previously reported,[21] catalytic systems prepared by mixing $[Rh(COD)_2]$-BF_4 and various bidentate phosphine[22] led to a considerable decrease in regioselectivity, albeit the overall product yields increased. Besides **2a** and **2a′** were also detected intractable aromatic side products (*vide infra*). Catalysis by Cp*Ru(cod)Cl provided **2a** and **2a′** in only 10% yield (1:4).

Then the scope of the reaction of **3** with terminal alkynes bearing various functionalities was assessed (Table 1). A

Scheme 1. Synthesis of Triyne 3

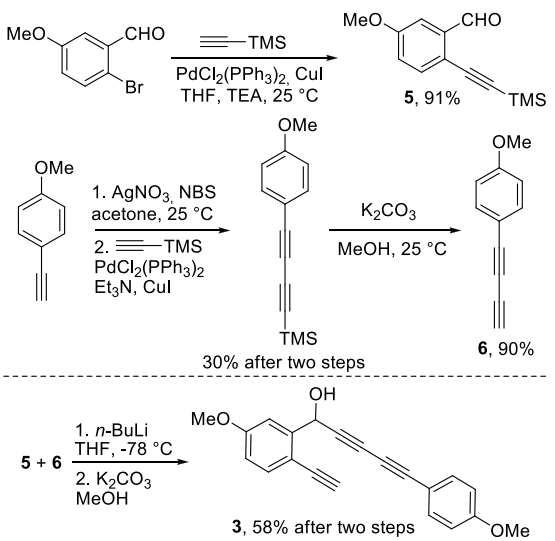
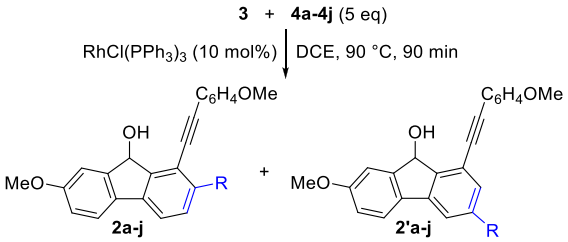


Table 1. Scope of Cyclotrimerization of 3 with Various Alkynes 4



entry	alkyne **4**	R	**2a**:**2′a** ratio	yield (%)[a]
1	**4a**	CH_2OH[b]	9.5:1	48
2	**4b**	CH_2OTBS	1.4:1	15
3	**4c**	CH_2OBz	5.6:1	52
4	**4d**	$C(Me)_2OH$	1.5:1	26
5	**4e**	CH_2CH_2OH	>99:1[c]	49
6	**4f**	$CH_2CH_2CH_2OH$	>99:1[c]	39
7	**4g**	CH_2NH_2	n.d.	0
8	**4h**	CH_2NHBz	13.1:1.	64
9	**4i**	COOEt	n.d.	0
10	**4j**	$SiMe_3$	6.8:1	12 (36)[d]

[a]Isolated yields. [b]Reaction carried out at 1.58 mmol scale. [c]"*meta* isomer" **2′** was not detected. [d]The overall yield could be improved by using 20 eq. of **4j**, at 25 °C and 20 h.

reaction with the TBS-protected propargyl alcohol **4b** gave the product in just 15% yield and poor regioselectivity (entry 2). The use of other catalytic systems did not improve the situation (see Table S2 in the SI for details). A reaction with propargyl benzoate (**4c**) gave desired products in 52% yield and a good **2c**:**2c′** ratio of 5.6:1 (entry 3). Using 2-methylbut-3-yn-2-ol (**4d**) resulted in a decrease in the yield of the desired product (26%) along with regioselectivity (**2d**:**2′d** = 1.5:1), presumably due to the steric hindrance of the alkyne (entry 4). When but-3-yn-1-ol **4e** and pent-4-ynol **4f** were engaged, the desired products were isolated as single regioisomers **2e** and **2f** in 49% and 39% yields, respectively (entries 5 and 6). A reaction with propargyl amine (**2g**) did not lead to any consumption of the starting material, probably due to the poisoning of the catalyst (entry 2). On the other hand, the use of *N*-propargyl benzamide (**2h**) led to a formation of desired product **2h** in 64% yield with very high selectivity for the "*ortho* isomer" (**2h**:**2′h** = 13.1:1) (entry 8). A reaction with ethyl propionate (**2i**) did not provide the expected product (entry 9). A reaction with trimethylsilyl ethyne (**4j**) yielded 12% of the desired cycloaddition products **2j** and **2j′** as the 6.8:1 mixture (entry 10). We also tested internal alkynes such

https://dx.doi.org/10.1021/acs.orglett.1c00519
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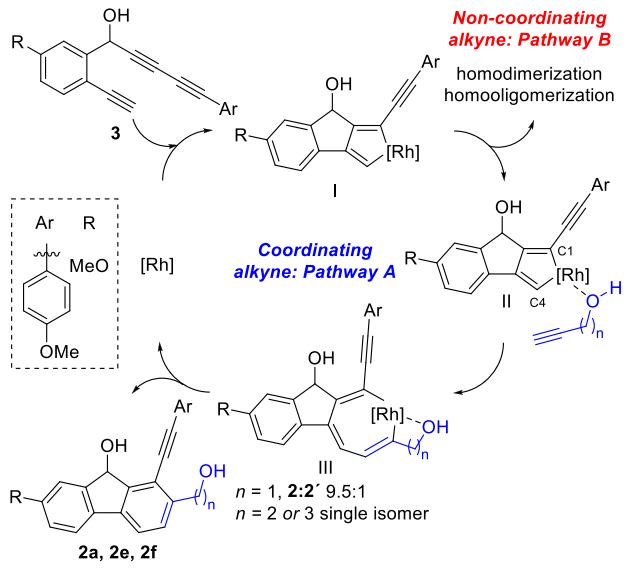
as 3-hexyne, 4-octyne, diphenylethyne, and but-2-yn-1-ol, but the reactions did not provide the desired products.

In all cases, except the reaction with propargyl amine (**4g**), the full consumption of **3** was observed, which led us to an assumption that **3** can undergo [2 + 2 + 2]-homocyclotrimerization. Thus, subjecting triyne **3** to the standard reaction conditions in the absence of the external alkyne led to full consumption of the starting material. Analyses (MS and NMR) of crude reaction mixtures as well as isolated material revealed the presence of inseparable mixtures of compounds corresponding to the dimers of **3**. The formation of similar species was also observed in cyclotrimerizations with internal alkynes. For the sake of accuracy, it cannot be excluded that some aromatic side products could be formed by dehydro-Diels–Alder reaction of triyne **3**.[23]

In accordance with the recently proposed mechanism involving coordination of Lewis basic functionalities by Tanaka[24] and Dudley[25] as the means of regiocontrol, we offer the following rationalization of the observed regioselectivity. After the initial formation of rhodacyclopentadiene **I** (Scheme 2), two competing reaction pathways can take place:

Scheme 2. Mechanistic Rational of the Observed Reactivity and Selectivity

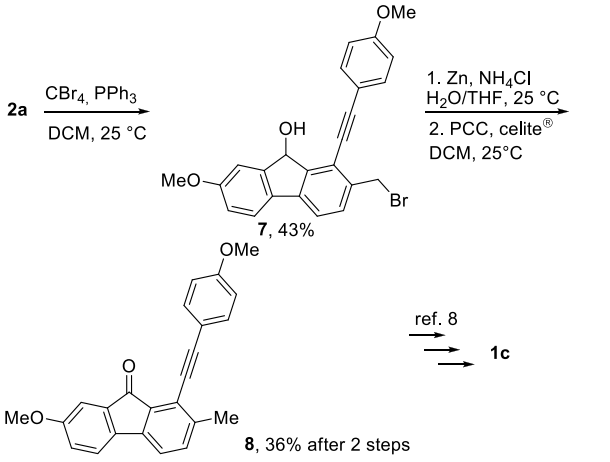


the desired pathway ***A*** leading to regioisomers **2** and pathway ***B*** giving rise to homodimers. It seems that the nature of the external alkyne **4** strongly influences the course of the reaction. The terminal alkynes containing in their structure a Lewis basic functionality bearing lone electron pairs undergo preferably the desired pathway ***A***. Two aspects can rationalize the high preference of the formation of the "*ortho*" regioisomers **2**. First, the insertion of the external alkyne takes place in a less sterically demanded C4–Rh vs C1–Rh bond (the fluorenol numbering, intermediate **II**, Scheme 2). Second, precoordination of the alkyne causes the correct orientation of the alkyne **II** and leads to the formation of the intermediate **III**, which upon the reductive elimination furnishes the desired product. This model reasonably explains exclusive "*ortho*" regioselectivity in the cyclotrimerization of homopropargyl alcohol (**2e**) and pent-4-ynol (**2f**) (entries 5 and 6) in comparison with propargyl alcohol (**2a**), its protected derivatives **2b** and **2c**, and 2-methylbut-3-yn-2-ol (**2d**) (entries 1–3 and 4). In the former two cases, intermediate **III** contains a thermodynamically stable five- or six-membered chelation ring, respectively. In contrast, alcohols **2a–2c** and **2d** form less stable four-membered chelation rings.

Moreover, steric hindrance in the case of 2-methylbut-3-yn-2-ol (**2d**) can lead to further destabilization of the intermediate and loss of the regioselectivity and the desired reactivity as well. The higher Lewis basicity of amides increases the ability to coordinate to the metal center compared to that of esters and can account for the higher regioselectivity: compare the reaction with *N*-propargyl benzamide (**2h**) and propargyl benzoate (**2c**) (entries 8 and 3). On the other hand, for sterically hindered terminal alkynes or the terminal alkynes without the polar moiety the homodimerization (pathway ***B***) is mostly observed. Internal alkynes proved to be not suitable alkynes for the desired transformation regardless of the polar moiety's presence or absence, perhaps due to the steric hindrance.

Then, we turned our attention to the synthesis of selaginpulvilins to demonstrate the versatility of the method (Scheme 3). We chose as synthetic targets selaginpulvilin C

Scheme 3. Formal Synthesis of Selaginpulvilin C



(**1c**), bearing the methyl group at C2 position, and selaginpulvilin D (**1d**), which does not bear any substitution at the C2 position. We commenced with the selaginpulvilin C (**1c**) synthesis by using compound **2a** bearing the hydroxymethyl group (Scheme 3). The initial attempts to directly reduce the hydroxymethyl moiety to the methyl group under various conditions failed. Pd-catalyzed reduction with triethylsilane[26] gave rise to a mixture of products that consisted of species with the reduced benzyl alcohol moiety and the reduced triple bond. Also, the use of a nickel chloride/sodium borohydride[27] system gave a complex reaction mixture. An attempt to employ Kursanov–Parnes reduction (triethylsilane/formic acid) gave rise to an intractable reaction mixture.[28] Finally, the reduction was brought about in the two-step process. First, the benzyl alcohol **2a** was converted to bromide **7** in 43% yield via the Appel reaction[29] (bromide **7** was not stable and underwent partially unspecified decomposition upon the chromatographic purification). Its immediate reduction with the zinc powder in a water/THF solution of NH_4Cl and subjecting the crude product to oxidation with PCC provided ketone **8** in 36% yield (after two steps). Ketone **8** is the known advanced intermediate in the synthesis of

https://dx.doi.org/10.1021/acs.orglett.1c00519
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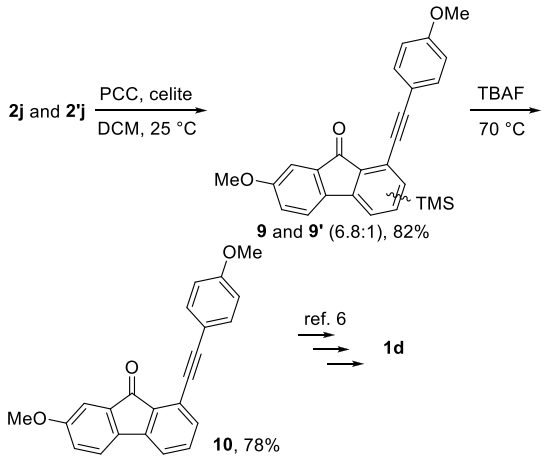
selaginpulvilin C (**1c**). Therefore, the formal synthesis of **1c** was accomplished.[8]

A mixture of regioisomeric trimethylsilylated fluorenols consisting of **2j** and **2′j** was used for the formal synthesis of selaginpulvilin D (**1d**), because the removal of the TMS group from both components would result in a single compound (Scheme 4). However, the low yield of the cyclotrimerization

Scheme 4. Formal Synthesis of Selaginpulvilins D



product **2j** and **2′j** prompted us to reinvestigate the reaction conditions (see Table S3 in the SI for details). Eventually, increasing the amount of trimethylsilyl ethyne from a 5- to 20-fold excess (with respect to **3**), lowering the reaction temperature to 25 °C, and prolonging the reaction time to 20 h gave a mixture of fluorenols **2j** and **2′j** in an improved yield of 36%. Subsequent oxidation of the fluorenol mixture with PCC furnished a mixture of fluorenones **9** and **9′** in 82% isolated yield. The formal synthesis of the selaginpulvilin D (**1d**) was concluded by desilylation of **9** and **9′** by TBAF at 20 °C to ketone **10** in 78% yield. Ketone **10** is the known advanced intermediate for the synthesis of selaginpulvilin D (**1d**).[6]

In summary, we have demonstrated that catalytic [2 + 2 + 2] cyclotrimerization of triyne **3** (1-(2-ethynyl-5-methoxyphenyl)-5-(4-methoxyphenyl)penta-2,4-diyn-1-ol) with selected terminal alkynes (propargyl alcohol and trimethylsilylethyne) is a suitable method for synthesis of intermediates **2a** and **2j** possessing the 1-alkynylfluorenol core of selaginpulvilins. Both intermediates were converted to the known advanced intermediates in selaginpulvilins C and D syntheses. The synthesis showcases the power of Rh-catalyzed intermolecular cyclotrimerizations to construct heavily substituted arenes selectively. Besides, it brings new information on the scope of catalytic [2 + 2 + 2] cyclotrimerization of diyne-ynes with terminal alkynes and ligand effect affecting its regioselectivity. The modular synthetic strategy allows accessing selaginpulviline analogues and further exploring the biological activities of this substance class.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00519.

All experimental procedures, compound characterization data, and copies of spectra (PDF)

FAIR data, including the primary NMR FID files, for compounds **2a**, **2′a**, **2b**, **2′b**, **2c**, **2d**, **2′d**, **2e**, **2f′**, **2h**, **2j**, **8**, **9**, and **10** (ZIP)

■ AUTHOR INFORMATION

Corresponding Author

Martin Kotora − *Department of Organic Chemistry, Faculty of Science, Charles University, 128 43 Praha 2, Czech Republic*; orcid.org/0000-0003-4491-7091; Email: kotora@natur.cuni.cz

Authors

Lukas Rycek − *Department of Organic Chemistry, Faculty of Science, Charles University, 128 43 Praha 2, Czech Republic*

Miguel Mateus − *Department of Organic Chemistry, Faculty of Science, Charles University, 128 43 Praha 2, Czech Republic*

Nela Beytlerová − *Department of Organic Chemistry, Faculty of Science, Charles University, 128 43 Praha 2, Czech Republic*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.1c00519

Author Contributions

‡M.M. and N.B. contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the Czech Science Foundation (Grant No. 18-17823S).

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https://dx.doi.org/10.1021/acs.orglett.1c00519
Org. Lett. XXXX, XXX, XXX−XXX