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Development of an Allenyne-Alkyne [4+2] Cycloaddition and its Application to Total Synthesis of Selaginpulvilin A

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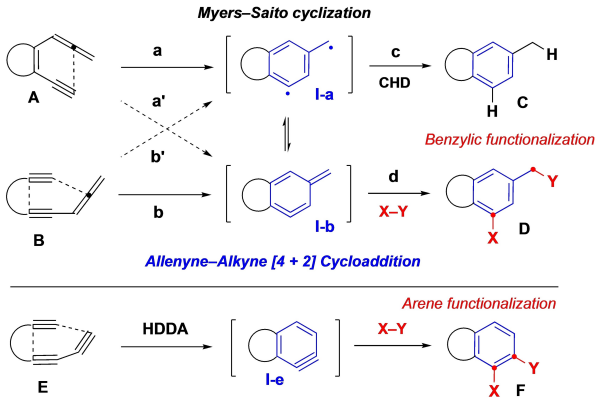
Abstract: A new [4+2] cycloaddition of allenyne-alkyne is developed. The reaction is believed to proceed with forming an α,3-dehydrotoluene intermediate. This species behaves as a σπ-diradical to react with a hydrogen atom donor, whereas it displays a zwitterionic reactivity toward weak nucleophiles. The efficiency of trapping α,3-dehydrotoluene depends not only on its substituents but also the trapping agents. Notable features of the reaction are the activating role of the extra alkyne of the 1,3-diyne that reacts with the allenyne moiety and the opposite mode of trapping with oxygen and nitrogen nucleophiles. Oxygen nucleophiles result in the oxygen-end incorporation at the benzylic position of the α,3-dehydrotoluene, whereas with amine nucleophiles the nitrogen-end is incorporated into the aromatic core. Relying on the allenyne-alkyne cycloaddition as an enabling strategy, a concise total synthesis of phosphodiesterase-4 inhibitory selaginpulvilin A is realized.

Introduction

The Myers–Saito cyclization (Scheme 1) refers to the cycloaromatization of enallene-alkyne such as **A** to form a 1,4-σπ-diradical intermediate **I-a**, which reacts with a hydrogen donor to generate arene product **C** (via path **a**–**c**).[1] Because of the relevancy of this aromatization process for the biological mode of action of anticancer natural products including neocarzinostatin[2] chromophore, extensive synthetic and mechanistic studies on this reaction have been reported.[3] Although diradical **I-a** reacts with hydrogen donor to generate **C**, in the presence of nucleophile, the reactivity of **I-a** is revealed as a zwitterion or as its resonance form α,3-dehydrotoluene[1b,4] **I-b**, leading to a benzylic carbon functionalized arene product **D** (path **a**–**d**). We speculated that the reaction of allenyne-alkyne **B** may provide an insight into the crossover between **I-a** and **I-b** believing that a concerted [4+2] cycloaddition of **B** will directly generate **I-b**. If this hypothesis proves to be true, **I-b** should provide not only arene **C** (via path **b**–**c**) by reacting with a hydrogen donor but also **D** (via path **b**–**d**) by reacting with a nucleophile. Alternatively, allenyne-alkyne **B** can undergo a stepwise cyclization (path **b**′) to form diradical **I-a**, thus merging the same manifold of reaction as **A**. This reactivity crossover between diradical[5] and zwitterion[6] depending on the trapping agent was observed in both the Myers–Saito[4] and Bergman[7] cyclization. Considering the structural and the mechanistic similarity between the two processes involving **A** and **B**, the [4+2] cycloaddition of allenyne-alkyne **B** can be considered as a pseudo-Myers–Saito cyclization.[8,9] The salient feature of this cycloaddition is the unique capability of benzylic functionalization as opposed to the arene functionalization by aryne intermediate **I-e** formed from hexadehydro Diels–Alder reaction (HDDA)[10] of triyne **E**.



Scheme 1. The relationship between the Myers–Saito cyclization and the allenyne-alkyne [4+2] cycloaddition.

Herein we describe our study on the [4+2] cycloaddition of allenyne-alkyne system **B**. Since the formation of α,3-dehydrotoluene **I-b** occurs under purely thermal conditions, the intrinsic reactivity of this species toward various trapping agents could be examined. To obtain general reaction profiles, structural variations are introduced to the parent allenyne-alkyne framework of **B** and the resulting α,3-dehydrotoluenes were trapped

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with alcohol, carboxylic acid, amine, and 1,4-cyclohexadiene. Finally, this new cycloaddition process was implemented in a synthetic strategy for a total synthesis of phosphodiesterase-4 inhibitory natural product selaginpulvilin A.[11]

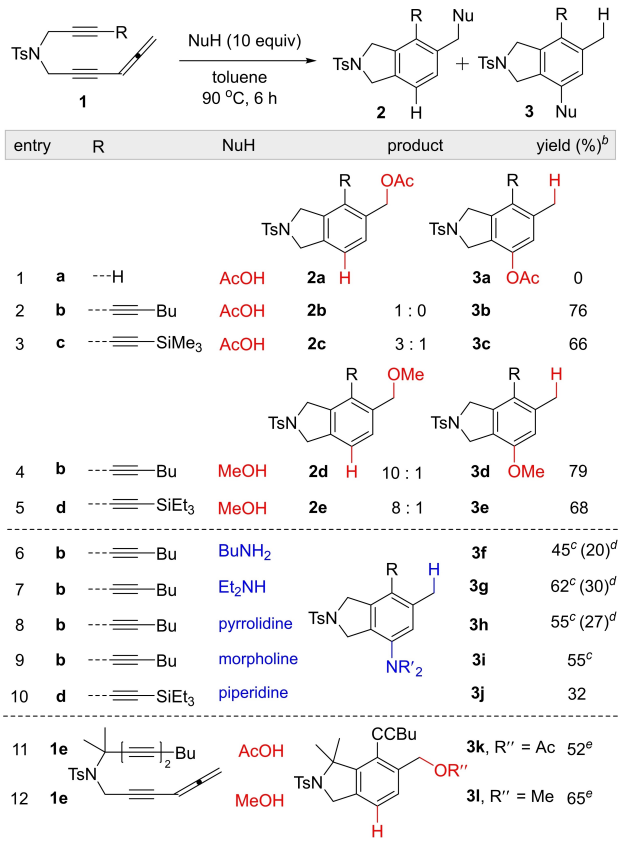
Results and Discussion

We commenced our investigation with a sulfoamide-tethered allenyne-alkyne **1a** containing a monosubstituted allene moiety (Table 1). When **1a** was heated at 90 °C in toluene along with AcOH (10 equiv) as trapping reagent, **1a** remained intact but led to decomposition on prolonged heating at higher temperature and there was no sign of forming **2a** or **3a** (entry 1). We speculated that introducing an extra alkynyl substituent on the terminal alkyne of **1a** would increase its reactivity as allenynophile based on the significant activating role of the extra alkyne in hexadehydro Diels–Alder reaction.[12] Gratifyingly, under otherwise identical conditions, **1b** containing an extra alkynyl substituent as a form of 1,3-diyne provided the AcOH-trapped product **2b** (76%), and its regioisomer **3b** was not detected (entry 2). The same reaction with **1c** containing a TMS group instead of a butyl group on the terminal alkyne afforded a mixture of **2c**/**3c** with a 3:1 ratio in 66% yield (entry 3). With MeOH as a trapping agent, the reaction of **1b** and **1d** provided a mixture of regioisomers **2d**/**3d** (10:1) and **2e**/**3e** (8:1) in 79 and 68% yield, respectively (entries 4 and 5). The decreased regioisomeric ratio of **2c**/**3c** and **2d**/**3d** caused by trimethyl and triethylsilyl substituent suggests that there should be a sizable steric interaction between these silyl groups and the incoming nucleophiles, which cannot be avoided.

The reaction with nitrogen nucleophiles including butylamine, diethylamine, piperidine, and morpholine were also examined (entries 6–10). These reactions provided single regioisomer of **3f**–**3j**, which contain the connectivity of the incorporated amine on the arene core rather than on the benzylic carbon. Also, it was found that the yields of these amine-incorporated products increased significantly when the reaction was performed at higher temperature (120 °C vs. 90 °C).[13] The effect of a *gem*-dimethyl substituent was examined with **1e**, which provided product **2f** and **2g** in 52 and 65% yield, respectively (entries 11 and 12). Contrary to the typical benefits of *gem*-dimethyl substituent effect for ring closure reaction,[14] the reaction of **1e** took longer (12 h) than **1b** (6 h) and the yield was also lowered for both AcOH and MeOH.

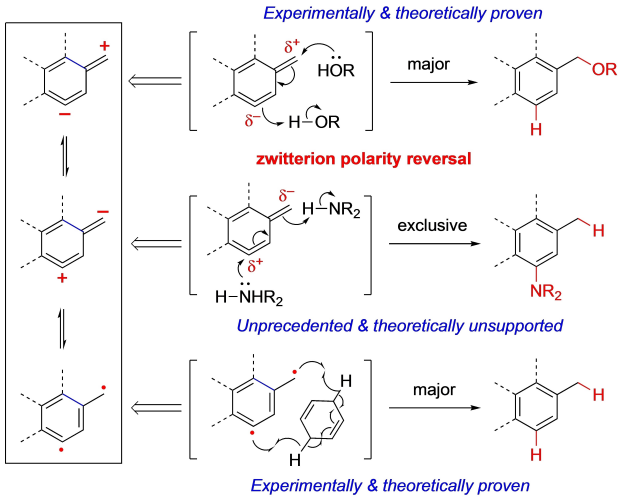
The opposite regioselectivity of trapping with oxygen and nitrogen nucleophiles seems to be correlated with their acidity (Scheme 2). Because of the relatively higher acidity of the oxygen-based nucleophiles (H_2O, MeOH, AcOH), the initial protonation preferentially occurs at the arene core of the α,3-dehydrotoluene with concomitant development of a cation character at the benzylic position, which then reacts with the oxygen-end of the nucleophiles to generate the observed products. Previous experimental and theoretical studies are consistent with this hypothesis.[4] On the other hand, nitrogen nucleophiles interact at the core of the α,3-dehydrotoluene with a developing anionic character at the benzylic carbon, which upon protonation leads the observed products.[15] In

Table 1. Alleyne-alkyne cycloaddition with a monosubstituted allene moiety.[a]



entry		R	NuH	product		yield (%)[b]
1	a	---H	AcOH	**2a** H	**3a** OAc	0
2	b	---Bu	AcOH	**2b**	1 : 0 **3b**	76
3	c	---$SiMe_3$	AcOH	**2c**	3 : 1 **3c**	66
4	b	---Bu	MeOH	**2d** H	10 : 1 **3d** OMe	79
5	d	---$SiEt_3$	MeOH	**2e**	8 : 1 **3e**	68
6	b	---Bu	$BuNH_2$		**3f**	45[c] (20)[d]
7	b	---Bu	Et_2NH		**3g**	62[c] (30)[d]
8	b	---Bu	pyrrolidine		**3h**	55[c] (27)[d]
9	b	---Bu	morpholine		**3i**	55[c]
10	d	---$SiEt_3$	piperidine		**3j**	32
11	1e		AcOH		**3k**, R″ = Ac	52[e]
12	1e		MeOH		**3l**, R″ = Me	65[e]

[a] 0.1 mmol scale of **1**. [b] Isolated yield. [c] Yield at 120 °C for 2 h. [d] Yields in the parenthesis are from reactions at 90 °C for 4 h. [e] Reaction time is 12 h.



Scheme 2. Reversal of the zwitterionic polarity of α,3-dehydrotoluene in trapping with oxygen and nitrogen nucleophiles and the diradical reactivity toward a hydrogen donor.

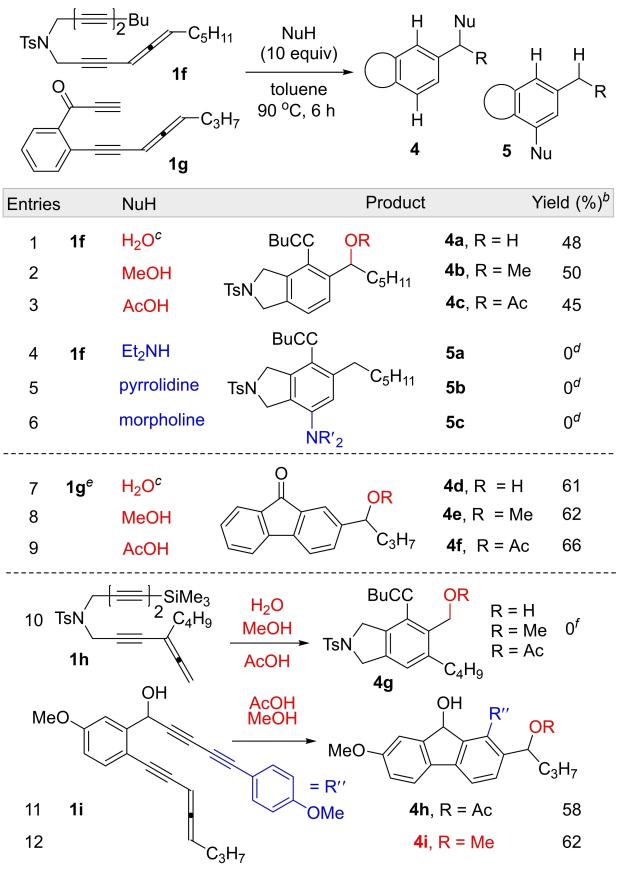
contrast with the oxygen trapping, the nitrogen trapping with the reversed polarity of α,3-dehydrotoluene has never been implicated in previous experimental and theoretical studies.[4] In the presence of a hydrogen donor such as 1,4-cyclohexadiene, α,3-dehydrotoluene behaves as a traditional 1,4-σπ-diradical (see Table 4).

Next, we examined the reactivity of allenyne-alkyne **1f** and **1g** containing a disubstituted allenyl moiety but differ by the tether element (Table 2). Under the standard conditions (90 °C in toluene, 6 h), the reaction of **1f** in the presence of H_2O, MeOH, and AcOH provided **4a** (48%), **4b** (50%) and **4c** (45%) as a single regioisomer (entries 1–3). Much to our surprise, however, the reactions with diethylamine, piperidine and morpholine failed in producing the products (**5a**–**5c**) and resulted in decomposition of **1f** (entries 4–6). This seems to be the consequence of the destabilization of the developing anionic character (Scheme 2) by the extra alkyl group on the benzylic carbon. The reaction of benzene-tethered substrate **1g** and H_2O, MeOH, and AcOH provide **4d** (61%), **4e** (62%), and **4f** (66%), respectively (entries 7–9). Yet again, trapping the α,3-dehydrotoluene intermediate derived from **1g** with diethylamine, pyrrolidine, morpholine, and butyl amine failed resulted in decomposition.

In addition, the reaction of allenyne-alkyne **1h** containing a butyl group on the internal carbon of the allene was unsuccessful even with oxygen nucleophiles (entry 14). At this point, the lack of reactivity of **1h** has no basis for rationalization. Trapping the intermediate derived from **1i** with AcOH and MeOH provided adducts **4h** and **4i** as a single regioisomer (entries 15 and 16).

The effect of substituents on the allene moiety was further examined with allenyne-alkynes **1j**–**1l** containing a trisubstituted allenyl group (Table 3). Running the reaction of **1j** and **1k** with H_2O (10 equiv) in CH_3CN provided water-trapped products **6a** (80%) and **6b** (62%) as a single regioisomer (entries 1 and 2). On the other hand, replacing H_2O with MeOH, the reaction of **1j** provided a mixture of MeOH adduct **6c** and alkene product **7c** in a 3:1 ratio (entry 3). In sharp contrast, the same reaction of **1j** but with *i*-PrOH and AcOH yielded only alkene product **7c** (entries 4 and 5). For the reaction with *i*-PrOH, it cannot be distinguished whether *i*-PrOH behaves as a proton donor to generate a *tert*-benzylic cation or as a hydrogen atom donor to generate the corresponding radical.[16] While the

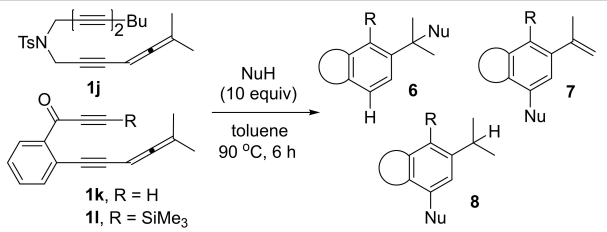
Table 2. Alleyne-alkyne cycloaddition with a disubstituted allene moiety.[a]



Entries		NuH	Product	Yield (%)[b]
1	**1f**	H_2O[c]	**4a**, R = H	48
2		MeOH	**4b**, R = Me	50
3		AcOH	**4c**, R = Ac	45
4	**1f**	Et_2NH	**5a**	0[d]
5		pyrrolidine	**5b**	0[d]
6		morpholine	**5c**	0[d]
7	**1g**[e]	H_2O[c]	**4d**, R = H	61
8		MeOH	**4e**, R = Me	62
9		AcOH	**4f**, R = Ac	66
10	**1h**	H_2O, MeOH, AcOH	**4g**, R = H / R = Me / R = Ac	0[f]
11	**1i**	AcOH, MeOH	**4h**, R = Ac	58
12			**4i**, R = Me	62

[a] 0.1 mmol scale of **1**. [b] Isolated yield. [c] CH_3CN is the solvent. [d] Decomposition at 90 °C. [e] Decomposition with diethylamine, pyrrolidine, morpholine, and butyl amine. [f] No reaction at 90 °C and decomposition on prolonged heating at 150 °C.

Table 3. Alleyne-alkyne cycloaddition with a trisubstituted allene moiety.[a]



entries		NuH	product		yield (%)[b]
1	**1j**	H_2O[c]	**6a**		80
2	**1k**	H_2O[c]	**6b**		62
3	**1j**[e]	CH_3OH	**6c**[d]	3 : 1	**7c** 78
4	**1j**	*i*-PrOH	**7c**		65
5	**1j**	AcOH	**7c**		75
6	**1k**[e]	CH_3OH	**6d**, R = H	5.5 : 1	**7d**, R = H 65
7	**1l**	CH_3OH	**6e**, R = $SiMe_3$		**7e**, R = $SiMe_3$ 0[f]
8	**1k**	AcOH			**7d** 45
9	**1l**	AcOH			**7e** 0[f]

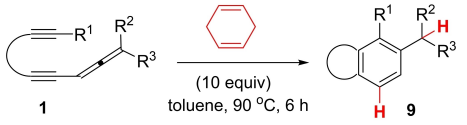
[a] 0.1 mmol scale of **1**. [b] Isolated yield. [c] CH_3CN is the solvent. [d] Contaminated with 6% of the other regioisomer. [e] Decomposition with diethylamine, pyrrolidine, morpholine, and butyl amine. [f] Decomposition at 90 °C.

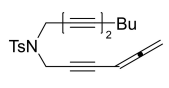
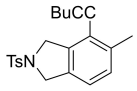
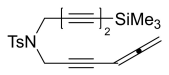
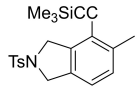
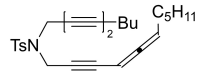
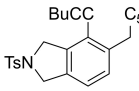
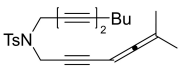
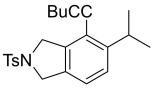
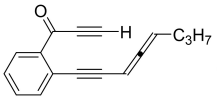
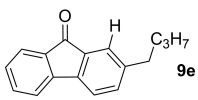
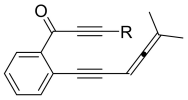
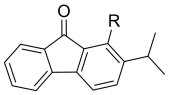
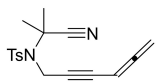
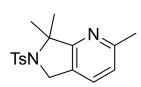
reaction of benzene-tethered substrate **1k** generated a mixture of **6d** and **7d** (5.5:1) in 78% yield in the presence of MeOH (entry 6), the corresponding silylated substrate **1l** failed in producing either **6e** or **7e** (entry 7). In the reaction with AcOH, **1k** generated only alkene product **7d** (45%) whereas **1l** led to decomposition without forming **7e** (entries 8 and 9). We believe that the TMS group in **1l** interferes with the initial formation of the α,3-dehydrotoluene intermediate due to the steric hindrance at the stage of the cycloaddition, not at the nucleophile trapping stage. Analogous to the reactivity of disubstituted allene-containing substrate **1f**, the reactions of **1j** and **1k** containing a trisubstituted allenyl moiety provided none of the amine adducts.

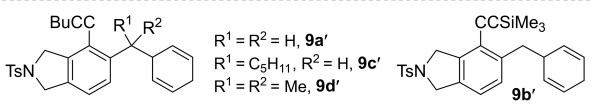
To test the hypothesis that α,3-dehydrotoluene **I-b** (Scheme 1) might reveal its reactivity through a diradical **I-a** in the presence of a hydrogen atom donor, we subjected allenyne-alkynes **1b**, **1c**, **1f**, **1g** and **1j**–**1l** to the standard reaction conditions along with 1,4-cyclohexadiene (Table 4). While substrates containing a mono, di, and trisubstituted allene moiety **1b**, **1c**, **1f**, and **1j** provided the expected dihydrogen adduct **9a**, **9b**, **9c** and **9d** along with the cyclohexadienyl adducts[1b,4c] **9a′**–**9d′** as a minor product (entries 1–4), the reaction of benzene-tethered substrates **1g**–**1l** failed in producing **9e**–**9g** (entries 5–7). The reaction with substrate **1m** containing a nitrile instead of a 1,3-diyne[17] also failed in producing **9h** (entry 8).

Based on these results, we envision that the unique cycloaromatization process can be exploited for a total synthesis of selaginpulvilins,[18] an alkynyl polyphenol natural product of *selaginella* family, which shows inhibitory activities (IC_{50} = 0.11–5.13 μM) against phosphodiesterase-4, a druggable target for treating asthma and chronic obstructive pulmonary disease.[11] Retrosynthetically, the fluorene core skeleton of selaginpulvilin A is planned to be installed via the cycloaddition of **12** with concomitant installation of the C-29 oxygen substituent (Scheme 3). A Sonogashira coupling of allenyl bromide **10**[19] with the known terminal alkyne **11**[18a] at low temperature (−20 °C)[20] provided **12** (59%), which was subjected to the established protocol with AcOH to generate fluorenol **13** (59%). Oxidation of the secondary alcohol **13** followed by removal of the TBS-group afforded phenylethylnyl-9*H*-fluorenone **14** (62%, 2 steps), which was treated with *p*-methoxyphenylmagnesium bromide to generate tertiary alcohol **15** (68%). Friedel–Crafts arylation of **15** to form **16** was interfered with double arylation but it was found that careful control of the reaction temperature at −20 °C suppressed the arylation at the benzylic carbon, generating **16** in 58% yield. Deprotection of the three methoxy and acetoxy groups from **16** was realized by treating with MeMgI in neat conditions at

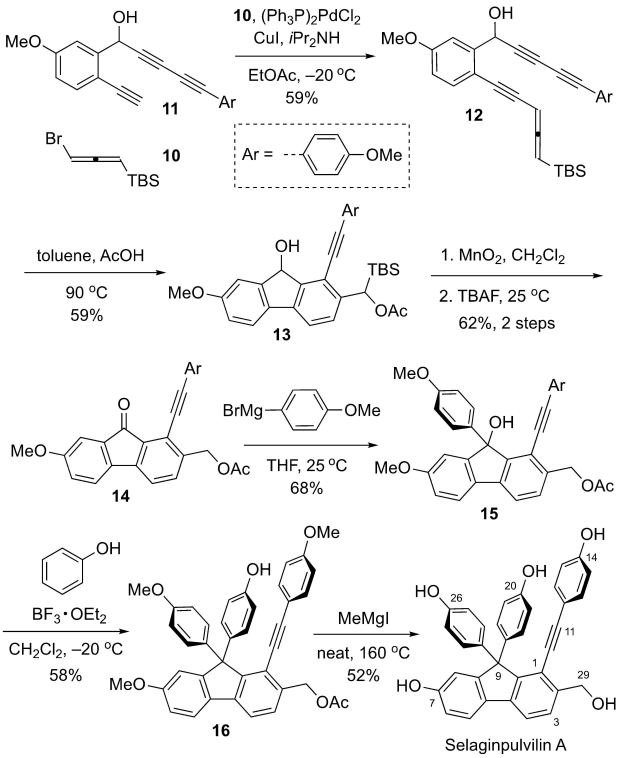
Table 4. Trapping α-3-dehydrotoluene containing a differently substituted allene moiety with hydrogen source.



entry		substrate	product		yield (%)[a]
1	**1b**			**9a**	66[b]
2	**1c**			**9b**	66[b]
3	**1f**			**9c**	61[b]
4	**1j**			**9d**	59[b]
5	**1g**			**9e**	0[c]
6	**1k**			**9f**, R = H	0[c]
7	**1l**			**9g**, $SiMe_3$	0[c]
8	**1m**			**9h**	0[c]



[a] Isolated yield. [b] Contaminated with 15% side products **9a′**–**9d′**. [c] Decomposition of the starting materials.



Scheme 3. Total synthesis of selaginpuvilin A.

160 °C to deliver selaginpulvilin A (52%). Compared to the previously reported hexadehydro Diels–Alder approach to the synthesis of selaginpulvilins,[18a] the current approach is more effective because the hydrogenation of an aryne intermediate can be avoided and the steps for introducing the C-29 oxygen functionality in the precursor can be minimized.

Conclusion

In conclusion, we developed a new [4 + 2] cycloaddition of allenyne-alkynes, which is a new variant of Myers–Saito cyclization. The reaction proceeds via forming an α,3-dehydrotoluene intermediate, which behaves as a zwitterion to react with various nucleophiles or 1,4-σπ-diradical in the presence of a hydrogen atom donor 1,4-cyclohexadiene. The efficiency of trapping the α,3-dehydrotoluene intermediates and the product distribution depends not only on the structure of α,3-dehydrotoluene but also on trapping agents. One of the most notable features of the allenyne-alkyne [4 + 2] cycloaddition is the significantly higher reactivity of 1,3-diyne as an allenynophile compared to the monoyne counterpart. Also, the opposite regioselectivity in trapping α,3-dehydrotoluene with oxygen and nitrogen nucleophiles is unique. Although the trapping behavior of oxygen nucleophile has been extensively studied and theoretically rationalized the trapping behavior of nitrogen showing the opposite regioselectivity is unprecedented. In general, oxygen nucleophiles such as alcohol and carboxylic acid results in the oxygen-end of the nucleophile incorporated at the benzylic position, whereas the nitrogen-end of the nucleophile is incorporated onto the aromatic ring. The prowess of the allenyne-alkyne [4 + 2] cycloaddition is demonstrated in a short total synthesis of selaginpulvilin A. The exact mechanisms for the formation of α,3-dehydrotoluene and its reactivity toward different reacting counterparts are currently under investigation.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

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[20] The allenyne moiety in **12** is prone to isomerize to the corresponding skipped 1,4-diyne moiety if the coupling reaction is carried out at ambient temperature.

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