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Convergent Assembly of Polycyclic Ethers via Acyl Radical Addition to Unactivated Enol Ether

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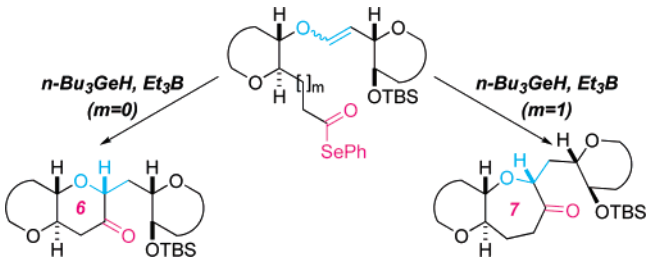
ABSTRACT



A new convergent strategy for assembling 6/6- and 6/7-fused ether ring systems was developed. The key features in our method include Ag^+-promoted facile formation of chemically labile enol ether from *O*,*S*-acetal and addition of an acyl radical to unactivated enol ether to cyclize a six- or seven-membered ether ring.

The *trans*-fused polyethers, represented by ciguatoxin (**1**, Figure 1)[1] and brevetoxin B (**2**),[2] are interesting natural products by virtue of their unusual ladder-shaped architecture, biological activity, and association with catastrophic phenomena such as seafood poisonings and red tides.[3] Their exquisitely complex structures have served as the inspiration for the development of new methodologies in organic synthesis.[4]

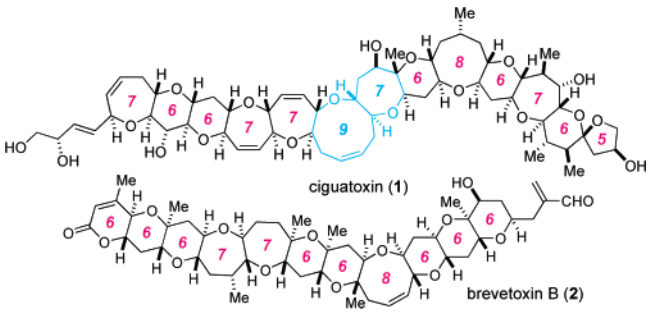


Figure 1. Representative natural polycyclic ethers.

Because the stepwise synthesis of more than 10 rings is practically impossible due to the large number of transformations required, the development of powerful methodologies for coupling substructures has been particularly important for the construction of gigantic molecules.[5] We previously

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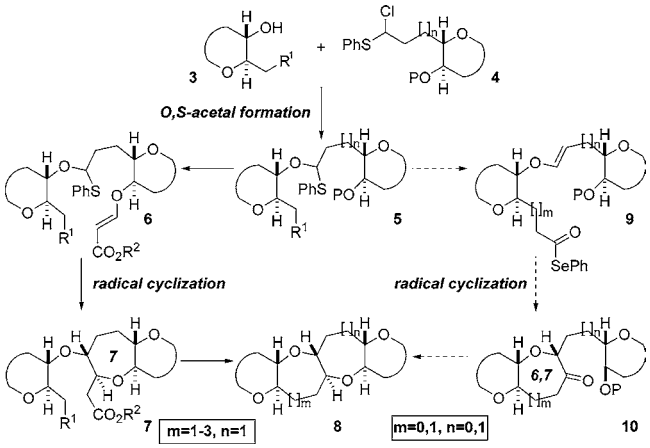
described the total synthesis of the three ciguatoxin congeners including **1** by utilizing a unified convergent strategy.[6] The corresponding two halves of **1** were assembled at the 9/7-ring system of the central portion (blue highlighting in Figure 1) via four key steps (Scheme 1): (i) coupling of the right

Scheme 1. Two Radical Routes to Assemble the Polyether Structure



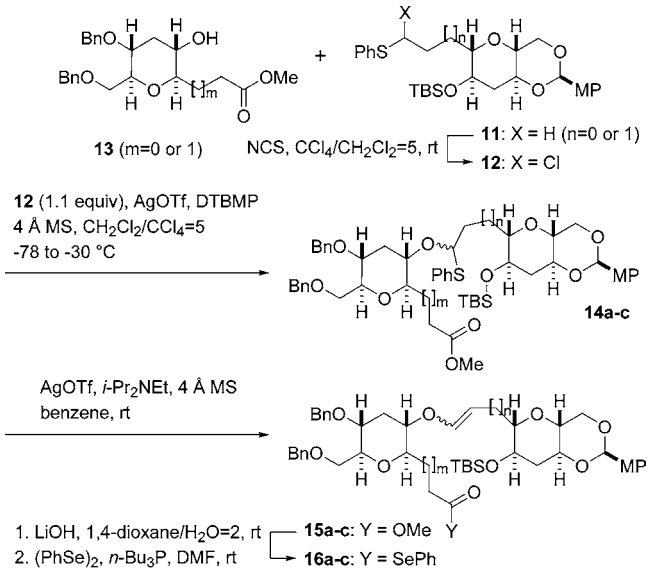
and left fragments by *O*,*S*-acetal formation (**3** + **4**→**5**);[7] (ii) introduction of β-alkoxyacrylate (**5**→**6**); (iii) seven-membered ring cyclization using *O*,*S*-acetal as a radical donor (**6**→**7**); and (iv) ring-closing olefin metathesis (RCM)[8] to build the nine-membered ring (**7**→**8**). Additionally, this protocol proved to be applicable to other 6/7,8,9/7/6-tetracyclic ring systems (**8**: $m = 1-3$; $n = 1$).[7b]

To increase the utility of the *O*,*S*-acetal coupling strategy, an alternative method was sought for assembling 6/6-, 7/6-, and 6/7-membered ring systems [**8**: $m = 0, 1$; $n = 0, 1$ (Scheme 1)] that are inaccessible through the radical cyclization/RCM sequence. These two methodologies would be complementary, and their combination would allow the construction of any typical ring system of natural ladder-shaped polycyclic ethers. Here, we report the development of a new method utilizing *O*,*S*-acetals as common intermediates.

As illustrated in Scheme 1, the mode of the radical cyclization differentiates the present method from the previous one. Thus, enol ether **9**, prepared from *O*,*S*-acetal **5**, was designed to be used as a radical acceptor. It was envisioned that an acyl radical, generated through homolytic cleavage of the C−Se bond of **9**, would react with the enol ether to afford the first six- or seven-membered ring of **10**.[9−11] Reductive etherification[12] from **10** would then give the second six- or seven-membered ring of **8**. Reaction from **9** to **10** was a particularly challenging step because of inefficient orbital interaction between the high SOMO of the nucleophilic acyl radical and the high LUMO of the electron-rich enol ether.[13] To develop the methodology, the tetracyclic ring systems were selected as target structures.

Synthesis of acyl radical cyclization of substrates **16a**−**c** began with tetrahydropyrans **11** ($n = 0$ or 1) and **13** ($m = 0$ or 1) (Scheme 2).[14] After treatment of phenylsulfide **11** with

Scheme 2. Formation of Enol Ethers from *O*,*S*-Acetals



m,n	yield of **14**	yield of **15**	yield of **16**
a: m=0, n=0	60% (dr=1.7:1)	92% (*cis*:*trans*=1:2.5)	95%
b: m=0, n=1	62% (dr=1.9:1)	94% (*cis*:*trans*=1.6:1)	95%
c: m=1, n=0	72% (dr=1.5:1)	95% (*cis*:*trans*=1:2.7)	95%

NCS,[15] the chloride of the resultant **12** was displaced by the hindered secondary alcohol of **13** by the action of AgOTf

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(13) Giese, B. *Angew. Chem., Int. Ed*. **1983**, *22*, 753.

(14) Compounds **11** and **13** were synthesized from 2-deoxy-D-ribose by a similar procedure that was described in ref 7b.

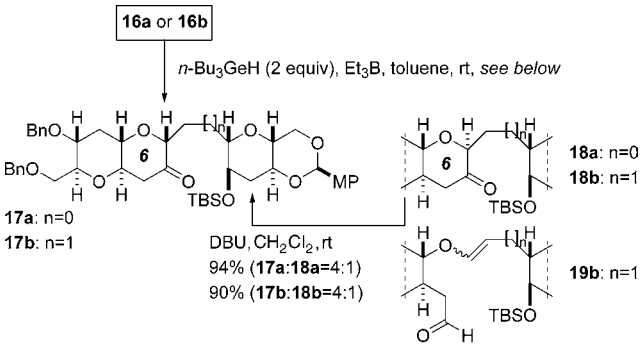
and 2,6-di-*tert*-butyl-4-methyl pyridine (DTBMP),[16] leading to coupling adduct **14** as a diastereomeric mixture. Enol ether formation then was realized using the same AgOTf in the presence of more basic *i*-Pr_2NEt.[17] Under these conditions, activation of the phenyl sulfide of **14** occurred to give acid-labile enol ether **15** in excellent yield. The geometric isomer ratio of **15** did not reflect the diastereomer ratio at the *O*,*S*-acetal carbon center of **14**, indicating an E1-like mechanism of the reaction. Finally, basic hydrolysis of methyl ester **15**, followed by phenylselenide introduction by the action of $(PhSe)_2$ and *n*-Bu_3P,[18] generated selenoester **16**. The high overall yields of the five-step sequence were indifferent to the number of the methylenes (*m*, *n* = 0, 1).

First, six-membered ring cyclization from **16b** was undertaken (Table 1). Upon exposure to *n*-Bu_3SnH/Et_3B[19] in benzene at room temperature (entry 1), the desired **17b** and its epimer **18b** were isolated in low yields, and a significant amount of aldehyde **19b** was obtained. The more reactive Ph_3SnH generated only **19b** (entry 2), indicating that the rate of acyl radical reduction exceeded that of the cyclization. To suppress premature reduction, $(TMS)_3SiH$ (entry 3) and *n*-Bu_3GeH[20] (entry 4) were used because these less-reactive hydrogen donors can be an advantage when the cyclization occurs slowly.[21] Both reagents produced the tetrahydropyran in high yield as a mixture of **17b** and **18b**; *n*-Bu_3GeH gave the better combined yield (entry 4). The optimized conditions also were applied successfully to **16a**, leading to **17a** and **18a** in 75% combined yield (entry 7). Importantly, the α-positions of ketones **18a** and **18b** were isomerized effectively with DBU to afford the desired isomers **17a** and **17b**, respectively.

To evaluate the stereochemical correlation between the geometrical isomers of **16** and the diastereomers **17** and **18**, chromatographically separated *cis*-**16** and *trans*-**16** were subjected independently to radical cyclization conditions. Interestingly, whereas the *cis*-isomers of **16a** and **16b** resulted only in the formation of the desired diastereomers **17a** and **17b**, respectively (entries 5 and 8), the *trans*-isomers generated an approximately 1:1 mixture of the diastereomeric tetrahydropyrans (entries 6 and 9).

Because of the success with this radical reaction, the same reaction conditions were applied to the more entropically disfavored seven-membered ring cyclization[22] (Table 2).

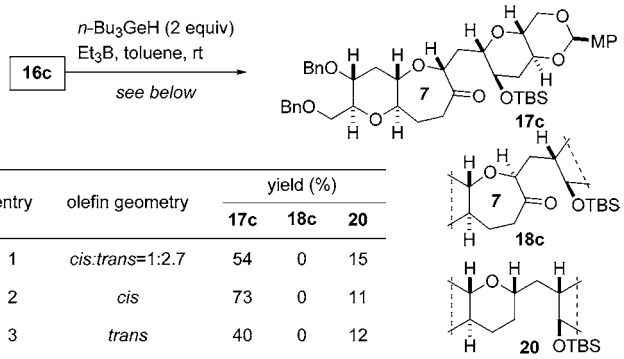
Table 1. 6-Exo Acyl Radical Cyclization



entry	substrate	olefin geometry	yield (%)		
			17	**18**	**19**
1[a]	**16b**	*cis*:*trans*=1:1	17	5	30[b]
2[c]	**16b**	*cis*:*trans*=1:1	0	0	60[d]
3[e]	**16b**	*cis*:*trans*=1.6:1	61	15	0
4	**16b**	*cis*:*trans*=1.6:1	65	13	0
5	**16b**	*cis*	78	0	0
6	**16b**	*trans*	41	38	0
7	**16a**	*cis*:*trans*=1:2.5	49	26	0
8	**16a**	*cis*	76	0	0
9	**16a**	*trans*	39	39	0

[a] *n*-Bu_3SnH was used as a hydrogen donor in benzene. [b] *cis*:*trans* = 1.5:1 [c] Ph_3SnH was used as a hydrogen donor in benzene. [d] *cis*:*trans* = 1.2:1 [e] $(TMS)_3SiH$ was used as a hydrogen donor in toluene.

Table 2. 7-Exo Acyl Radical Cyclization



entry	olefin geometry	yield (%)		
		17c	**18c**	**20**
1	*cis*:*trans*=1:2.7	54	0	15
2	*cis*	73	0	11
3	*trans*	40	0	12

Remarkably, *n*-Bu_3GeH and Et_3B converted **16c** into cyclized product **17c** in 54% yield with complete stereochemical control (entry 1). A small amount of tetrahydropyran **20** was formed in this reaction; competing decarbonylation of the acyl radical produced the corresponding alkyl radical that reacted with the enol ether. Despite this minor path, stereocontrolled intramolecular addition to the electron-rich

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(21) Rate constants for the reaction of primary alkyl radicals with Group 14 hydrides (M^{-1} s^{-1} at 80 °C): Ph_3SnH (2.2×10^7) > *n*-Bu_3SnH (6.4×10^6) > $(TMS)_3SiH$ (1.2×10^6) > *n*-Bu_3GeH (3.4×10^5). (a) Chatgilialoglu, C.; Newcomb, M. *Adv. Organomet. Chem.* **1999**, *44*, 67. (b) Chatgilialoglu, C. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: 2001; Chapter 1.3, pp 28−49.
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alkene to form oxepane is noteworthy and highlights the versatility of our reaction. Interestingly, the *cis*-isomer of **16c** (entry 2) gave a greater yield of **17c** in comparison to the *trans*-isomer (entry 3).

The stereoselectivity of both the six- and seven-membered ring cyclizations is explained as shown in Figure 2. The

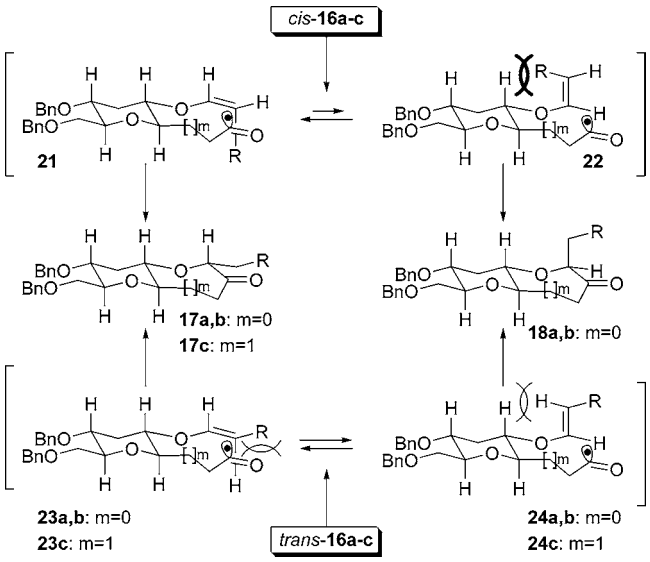
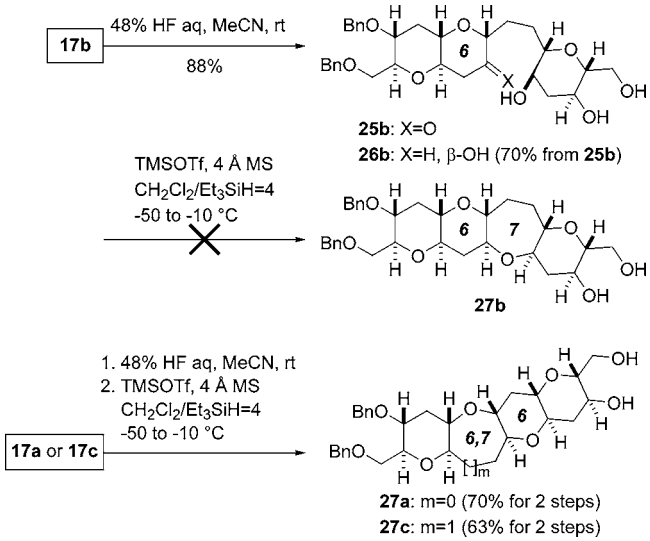


Figure 2. Mechanistic rationale for the acyl radical cyclization.

exclusive stereoselectivity for **17** observed in the cyclization of *cis*-**16** (Table 1, entries 5 and 8; Table 2, entry 2) is the result of the strongly favored transition state **21** with the s-*trans*-conformation to alleviate severe $A^{1,3}$-type allylic strain of the bulky R group in the transition state **22**. In contrast, both conformational isomers **23** and **24**, generated from *trans*-**16**, encounter unfavorable steric interactions; the interaction between the oxygen and R for **23** and the $A^{1,3}$-type allylic strain of the hydrogen for **24**. The nonselective formation of **17a**/**b** and **18a**/**b** from *trans*-**16a**/**b** suggests that the energy difference between **23a**/**b** and **24a**/**b** is negligible for the six-membered ring formation (Table 1, entries 6 and 9). In contrast, **23c** appears to be more stable than **24c** because of the exclusive formation of **17c** from *trans*-**16c**, yet the cyclization from **23c** is less efficient than that from **21**, presumably due to the steric repulsion in **23c** (Table 2, entry 2 vs 3). The different stereochemical outcomes of *trans*-**16a**/**b** and *trans*-**16c** indicate that the number of the methylenes influences the three-dimensional interaction of the radical acceptor and the donor in the transition state.

To complete our model investigation, our focus turned to syntheses of the tetracyclic ether systems (Scheme 3). Disappointedly, reductive etherification of hydroxyketone

Scheme 3. Synthesis of Tetracyclic Ethers



25b, prepared from **17b**, failed to give oxepane **27b**. The main product in this reaction was the reduced, open-chain diol **26b**. In contrast, reductive etherification successfully produced tetrahydropyran rings in **27a** and **27c**. Treatment of **17a** with aqueous HF simultaneously removed the TBS and *p*-methoxybenzylidene groups to afford the hemiacetal, which was converted into the 6/6/6/6-ring system **27a** by the action of TMSOTf and Et_3SiH. Application of the same protocol to **17c** resulted in synthesis of the 6/7/6/6-ring system **27c**, which is the pseudoenantiomeric compound of **27b**. These results provided valuable insights into the cyclization strategy, revealing the desirability of constructing the seven-membered ring by radical cyclization rather than by the reductive etherification for synthesis of the 6/7-ring systems.

In summary, we have devised the new, efficient convergent assembly of polycyclic ethers via acyl radical cyclization. The neutral reaction sequence would enable syntheses of any 6/6- or 6/7-ring system of natural polycyclic ethers with sensitive functional groups. Furthermore, the use of the unactivated enol ethers as radical acceptors should find wide application in organic synthesis.

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Supporting Information Available: Experimental procedures and spectroscopic data for synthetic compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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