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Novel Assembly of Cyclic Ethers by Coupling α-Chlorosulfides and Alcohols

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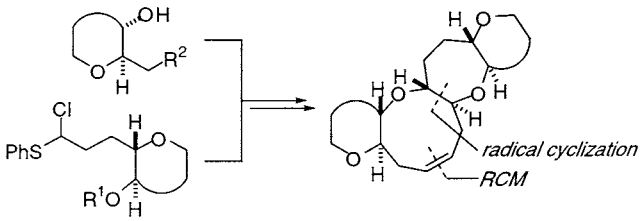
ABSTRACT



A novel protocol for assembling polycyclic ethers was developed and successfully applied to the synthesis of the EFGH ring system of ciguatoxin CTX3C. A key transformation involves construction of an *O*,*S*-acetal through coupling of α-chlorosulfide and a secondary alcohol under mild conditions. The method is highly applicable to use with sensitive substrates and will enable the synthesis of various natural and artificial polycyclic ethers.

Recently, many ladder-shaped polyethers have been isolated from marine sources and their structures determined by extensive modern spectroscopic techniques using minute amounts of the materials.[1] Their most notable structural feature lies in their long semirigid architectures comprising trans/syn-fused ether rings of various sizes. Ciguatoxins (CTXs),[2] a representative collection of ladder-shaped polyethers, have received much attention among chemists and biologists, as such polyethers have been found to cause widespread seafood poisoning known as ciguatera[3] and bind to the voltage-gated sodium channel at picomolar concentrations.[4] To supply ciguatoxins for further studies, we launched a project into their total synthesis over 10 years ago[5,6] and very recently achieved the synthesis of ciguatoxin CTX3C (**1**, Figure 1).[7]

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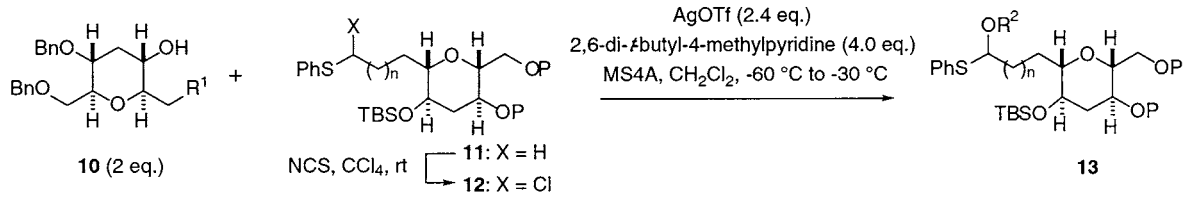
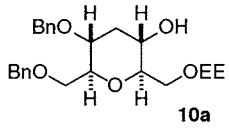
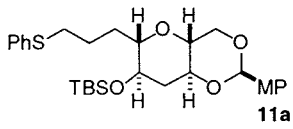
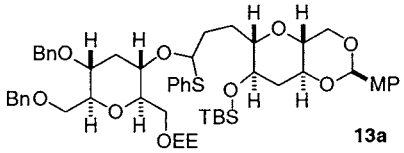
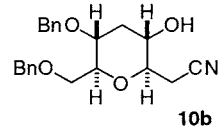
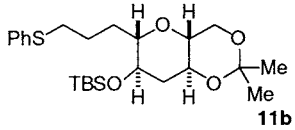
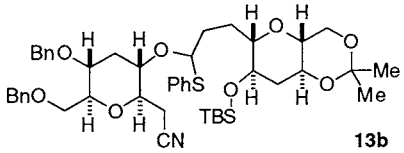
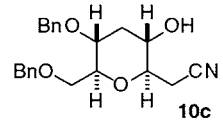
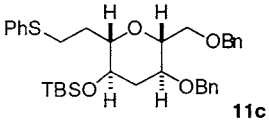
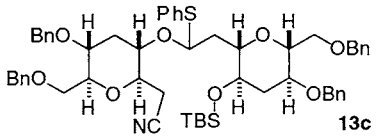
Table 1. Construction of *O*,*S*-Acetal from α-Chlorosulfide



alcohol	alkylsulfide	coupling product	yield from **11** (diastereomer ratio)
 **10a**	 **11a**	 **13a**	86% (2:1)
 **10b**	 **11b**	 **13b**	80% (1:1)
 **10c**	 **11c**	 **13c**	65% (1:1)

Our synthesis relied on the highly convergent strategy of assembling simple cyclic ethers. The final stage involved coupling between the A−E ring[5e] and the H−M ring systems[5f] with subsequent construction of the central FG ring system (Figure 1).[5d,7,8] This strategy is applicable to all

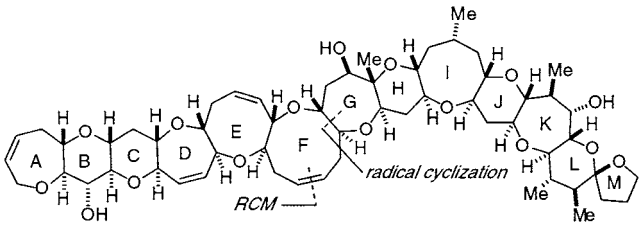
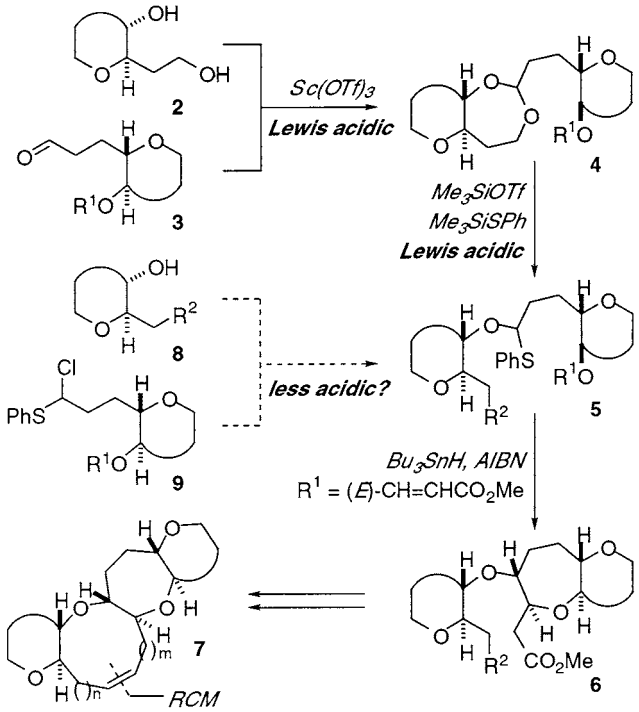


Figure 1. Structure of ciguatoxin CTX3C (**1**).

ciguatoxins, because they all have the FG ring structure in common.[2] To combine the fragments,[5d,7,8] four key transformations were used, which are shown schematically in Scheme 1: (i) coupling of the right and left fragments by acetalization using $Sc(OTf)_3$ (**2** + **3** → **4**);[9] (ii) Lewis acid-mediated *O*,*S*-acetal formation (**4** → **5**); (iii) radical cyclization to the seven-membered ring (**5** → **6**);[10−12] and (iv) ring-

Scheme 1. Schematic Presentation of Previous and New Coupling Methods



(8) (a) Sasaki, M.; Noguchi, T.; Tachibana, K. *Tetrahedron Lett.* **1999**, *40*, 1337; (b) *J. Org. Chem.* **2002**, *67*, 3301.

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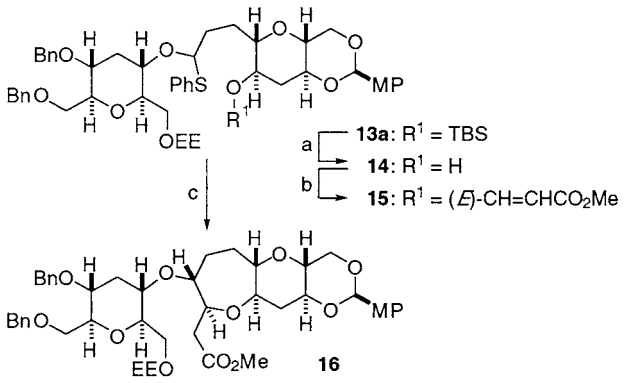
Scheme 2[a]

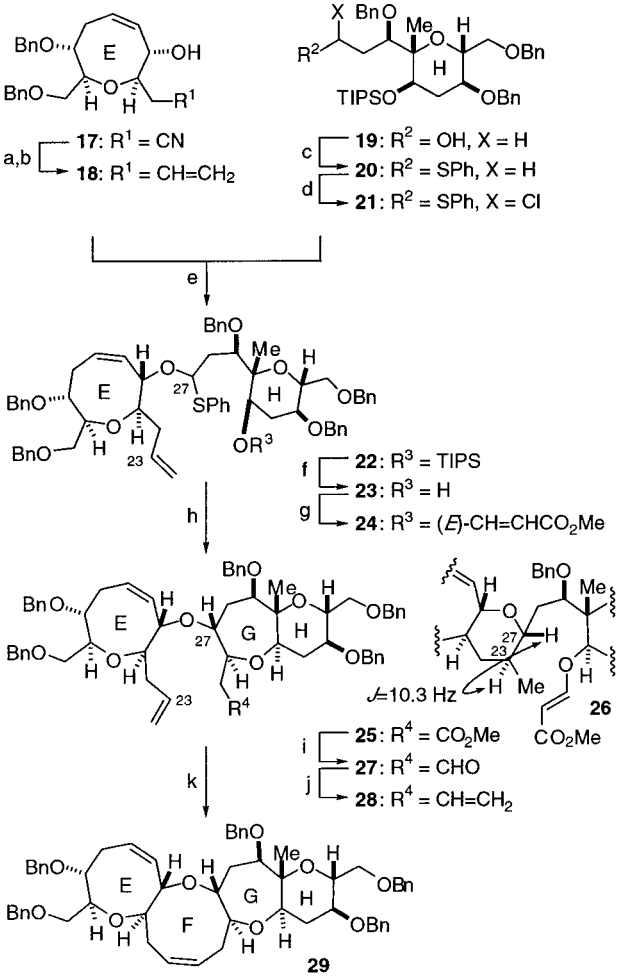


[a] Reaction conditions: (a) TBAF, THF, rt; (b) methyl propiolate, 4-methylmorpholine, CH_2Cl_2, 82% (two steps); (c) *n*-Bu_3SnH, AIBN, toluene, 80 °C, 92%.

closing olefin metathesis reaction (RCM)[13] to build the nine-membered ring (**6** → **7**). Although this sequence was successfully applied to the total synthesis of CTX3C, the Lewis acid nature of the first two reactions (i and ii) restricts the protective group strategy, and potentially causes problems in synthesizing CTX congeners as well as other natural and artificial polyethers. We therefore decided to develop a new route to *O*,*S*-acetal, without the need for strongly acidic conditions, which would further expand the applicability of the strategy to multisensitive functionalities. Here we report a mild method of constructing *O*,*S*-acetals, the syntheses of model compounds, and the EFGH ring system of CTX3C itself.

Our alternative synthetic strategy relied on the direct construction of the *O*,*S*-acetal **5** by coupling secondary alcohol **8** and α-halosulfide **9** (Scheme 1). This type of reaction was developed by Mukaiyama et al.[14] and recently further explored by the Hindsgaul group[15] in the context of their syntheses of oligosaccharides. The obtained **5** would be readily subjected to the radical cyclization to form the seven-membered ring (**5** → **6**). One important aspect of the strategy is that the stereoselective synthesis of the *O*,*S*-acetal

Scheme 3[a]



[a] Reaction conditions: (a) DIBAL, CH_2Cl_2, −78 °C, 100%; (b) CH_3PPh_3Br, $NaN(SiMe_3)_2$, THF, from 0 °C to rt, 95%; (c) $(PhS)_2$, *n*-Bu_3P, pyridine, rt, 100%; (d) NCS, CCl_4, rt; (e) **18** (2.5 equiv), AgOTf (1.5 equiv), 2,6-di-*tert*-butyl-4-methylpyridine (2.0 equiv), CH_2Cl_2, from −50 °C to −30 °C, 70% from **20**, 96% recovery of **18**; (f) TBAF, THF, rt, 87%; (g) methyl propiolate, 4-methylmorpholine, CH_2Cl_2, 100%; (h) *n*-Bu_3SnH, AIBN, toluene, 80 °C, 82% (**25**:**26** = 2.1:1); (i) DIBAL, CH_2Cl_2, −90 °C; (j) CH_3PPh_3Br, $NaN(SiMe_3)_2$, THF, from 0 °C to rt, 54% from a mixture of **25** and **26** (two steps); (k) $(PCy_3)_2Cl_2Ru$=CHPh (30 mol %), CH_2Cl_2 (0.01 M), reflux, 3 h, 100%.

of **5** is not necessary, because the stereochemical information of the radical precursor is usually lost upon formation of the radical. Halophilic activators such as the silver cation for the coupling are highly chemoselective and nonacidic, allowing the use of a wide variety of protective groups in a multifunctional system. There are also fewer synthetic steps from the coupling reaction than in the previous method because it is not necessary to proceed via *O*,*O*-acetal **4**.

First, we applied the coupling sequence to model compounds with hydroxyl groups masked by various protective groups (Table 1). The substrates used here (**10**, **11**) were prepared from 2-deoxy-D-ribose via standard synthetic manipulations.[16] The sulfide **11** was treated with *N*-chlorosuccinimide in CCl_4 to install chloride under neutral condi-

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(14) Mukaiyama, T.; Sugaya, T.; Marui, S.; Nakatsuka, T. *Chem. Lett*. **1982**, 1555.

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tions,[14,17] and the obtained α-chlorosulfide **12** was activated by silver triflate, in the presence of 2,6-di-*tert*-butyl-4-methylpyridine as a buffer, to give the desired *O*,*S*-acetal **13** in good yield.[15b] The thioalkyl group of **13**, which could be potentially activated by silver salt, was stable under the coupling conditions. While acid-sensitive acetal-type protective groups were not usable with the previous strategy, ethoxyethyl (EE), *p*-methoxyphenyl (MP) acetal (**13a**), and acetonide (**13b**) are compatible with the present reaction conditions, clearly demonstrating the advantage of this method.

To test seven-membered ring formation, compound **13a** was chosen for further synthetic transformations (Scheme 2). First, the TBS ether **13a** was converted to β-alkoxyacrylate **15** via a two step sequence: (i) TBAF, THF; (ii) methyl propiolate, 4-methylmorpholine, CH_2Cl_2.[11a] Treatment of **15** (a 2:1 mixture of diastereomers) with *n*-Bu_3SnH in the presence of AIBN at 80 °C gave the seven-membered ring as a single diastereomer in 92% yield.[10] Thus, as expected, the chirality of the acetal carbon is indifferent to the stereoselectivity of the radical cyclization. Since construction of a medium-sized ring by RCM of an O-linked oxacycle such as **16** is well established,[5,7,8,18,19] this synthesis is readily applicable to the synthesis of 6−*x*−7−6 ring systems.

Having successfully developed a novel strategy for forming *O*,*S*-acetals, we turned our attention to the synthesis of the EFGH ring system as a model study of the total syntheses of ciguatoxins (Scheme 3). The E-ring **17**[5d] and the H-ring **19**[5d,8] were prepared using the previously published procedures. Nitrile **17** was converted to the E-ring olefin **18** via DIBAL reduction and subsequent Wittig olefination (95% yield). The phenylthio group was introduced to **19** using $(PhS)_2$ and Bu_3P in pyridine to afford **20** in quantitative yield.[20] Treatment of **20** with NCS in CCl_4 led to the α-chlorosulfide **21**, and then the crude **21** was immediately coupled with 2.5 equiv of **18** by silver triflate to give the *O*,*S*-acetal **22** in 70% yield as a single diastereomer. The TIPS group of **22** was removed with TBAF to give the secondary alcohol **23**, which was converted to the β-alkoxyacrylate **24** using methyl propiolate and 4-methylmorpholine in 87% yield.[11a] Subjecting **24** to the radical cyclization allowed the G ring to be constructed stereoselectively to afford **25** as an inseparable mixture with **26** arising from the 6-exo cyclization to the terminal olefin (**25**:**26** = 2.1:1, 82% yield). DIBAL reduction of the mixture, followed by methylenation, gave pure diene **28** in 54% yield for the two steps. Finally, RCM of **28** using Grubbs catalyst[21] formed the nine-membered F ring to afford quantitatively the EFGH ring system **29**. Although the regioselectivity of the radical cyclization (**24** → **25**) should be optimized, the transformations from the coupling reaction require only 8 steps (previously 12 steps were required).[5d]

A novel coupling protocol for rapidly constructing polycyclic ethers was developed, and we have demonstrated the application of this method to the EFGH structural fragment of CTX3C. The neutral nature and high chemoselectivity of the coupling protocol will enable the synthesis of a wide variety of substrates having acid-sensitive functionality. Further studies toward the synthesis of ciguatoxins and artificial polyether compounds with biological importance are currently underway in our laboratory.

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

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(16) Preparation of **11a**−**c** will be described in a full account. A similar compound has previously been prepared from 2-deoxy-D-ribose; see: Fuwa, H.; Sasaki, M.; Tachibana, K. *Tetrahedron* **2001**, *57*, 3019.

(17) For a review on α-chlorosulfides, see: Dilworth, B. M.; McKervey, M. A. *Tetrahedron* **1986**, *42*, 3731.

(18) Oishi, T.; Nagumo, Y.; Hirama, M. *Chem. Commun*. **1998**, 1041.

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(20) Nakagawa, I.; Hata, T. *Tetrahedron Lett.* **1975**, *17*, 1409.

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