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A new synthesis of key intermediates for the assembly of polycyclic ethers: $Yb(OTf)_3$-promoted formation of *O*,*S*-acetals from α-fluorosulfides and alcohols

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Abstract—We report a new reaction for the direct construction of *O*,*S*-acetals, key intermediates in the assembly of fused polycyclic ethers. α-Fluorosulfides and secondary alcohols were coupled by the action of $Yb(OTf)_3$ to generate *O*,*S*-acetals in high yield. The neutral and selective nature of the reaction should be useful for synthesizing natural and artificial polyethers with multisensitive functionalities.

With their imposing molecular structure, the ladder-shaped polyethers pose considerable challenge to synthetic chemists.[1] Ciguatoxins have one of the most complex structures among this class of natural products,[2] and have attracted intense attention from the chemical community.[3] In 2001, we reported the first total synthesis of ciguatoxin CTX3C[2b] (**1**, Fig. 1), which was further improved in 2002 utilizing a new protective group strategy.[4]

In our convergent synthesis of CTX3C, the most challenging coupling is the final one, whereby the left (AB-CDE) and right (HIJKLM) ring systems are joined with the simultaneous construction of the FG-ring. As schematically shown in Scheme 1, this protocol used *O*,*S*-acetal **8** as a key intermediate, from which the G ring and the F ring were constructed through radical cyclization[5] and the ring-closing olefin metathesis reaction,[6] respectively (**8** → **9** → **10**). The *O*,*S*-acetal **8** was produced by two Lewis acid-mediated reactions: acetalization of the fragments **2** and **3**, and subsequent introduction of thiophenyl to **4**.[7]

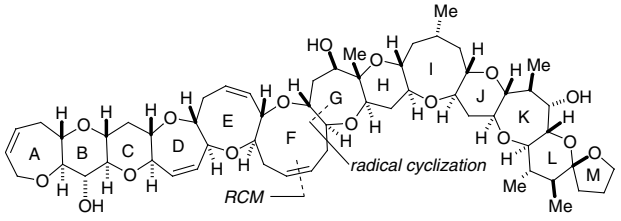

Figure 1. Structure of ciguatoxin CTX3C (**1**).

Very recently, we have developed a more direct method to form *O*,*S*-acetal (Scheme 1). In this strategy, sulfide **6** is converted to α-chlorosulfide **7** using NCS, and then **7** is activated using AgOTf in the presence of secondary alcohol **5** and base to form the *O*,*S*-acetal **8**. This procedure is clearly advantageous for the synthesis of complex substrates because of its neutral reaction conditions, and has been successfully applied to the EFGH-ring fragment of CTX3C[8] and 6-X-7-6 ring systems of various ring sizes (X = 7–9).[9] In light of the importance of the mixed acetal strategy for synthesizing polyether structures, we have become interested in expanding further its potential using alternative methods. This paper reports the development of a new reaction to form *O*,*S*-acetals from α-fluorosulfides.

We first targeted compound **15** (Table 1), which previously was synthesized from chlorosulfide **14**, and which can be converted to the EFGH-ring system **16** in 6

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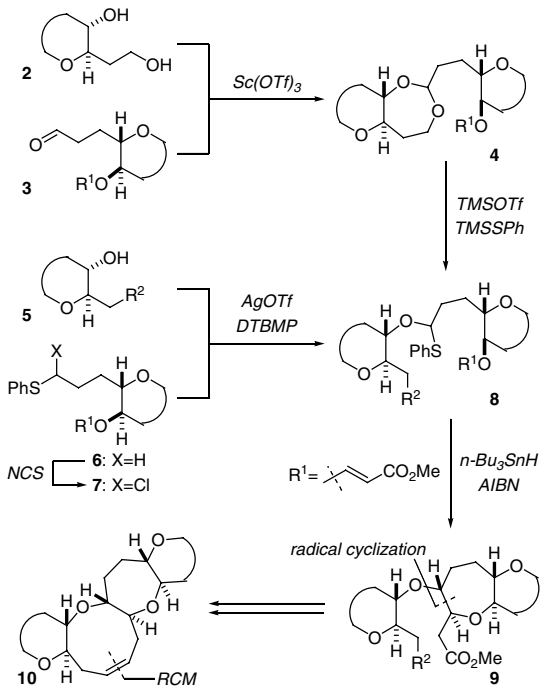


Scheme 1. Schematic presentation of two coupling methods: DTBMP = 2,6-*tert*-butyl-4-methylpyridine.

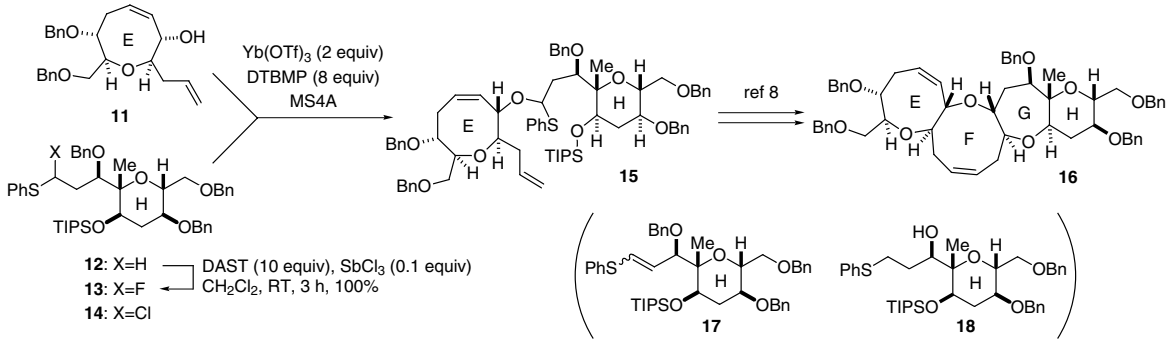
synthetic steps.[8] The new synthesis of **15** involved initial fluorination of sulfide **12** by applying the conditions developed by Robins.[10] A reagent combination of (diethylamino)sulfur trifluoride (DAST) and catalytic $SbCl_3$ in CH_2Cl_2 converted **12** to α-fluorosulfide **13** in 100% yield as a diastereomeric mixture (5:4). In sharp contrast to the instability of the corresponding chloride **14**, fluoride **13** was chemically stable and isolable in pure form using silica gel chromatography.

After screening reagents and conditions, it was found that $Yb(OTf)_3$ effectively induced coupling of the stable fluoride **13**, even at low temperatures (Table 1).[11,12] The desired *O*,*S*-acetal **15** was produced by treating fluoride **13** with $Yb(OTf)_3$ (2 equiv) in the presence of alcohol **11** (1.2 equiv), 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP, 8 equiv) and molecular sieves 4A (MS4A). The yield and time of reaction depended considerably on the solvent (entries 1–4). The reaction in CH_2Cl_2 was sluggish and low yielding for the practical purposes, but THF and DME appear to be promising media. Although the target product **15** was obtained, significant formation of byproducts **17** and **18** was problematic. As illustrated in Scheme 2, compounds **17** and **18** are considered to arise from HF-elimination and from an intramolecular hydride shift from the benzylic position, respectively, upon fluoride activation of **13**.

To accelerate the intermolecular reaction over the self-consumption of **13**, the reaction concentration of **13** was doubled in DME (Table 1, entry 5), which provided an improved yield of **15** with less byproducts. The best yield of **15** was achieved (79%, a 5:1 diastereomer ratio,[13] entry 6), when the amount of alcohol **11** was increased to 2 equiv and the concentration of **13** was 100 mM in DME.

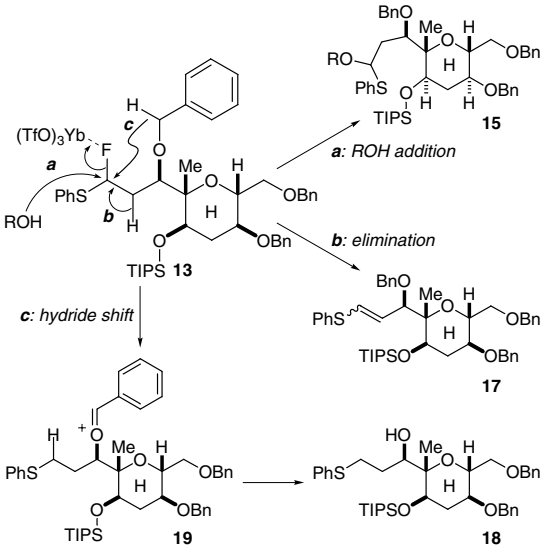
Having successfully established the new coupling procedure, we then targeted the acetal-protected sulfide **20** to investigate whether the method is suitable for acid

Table 1. $Yb(OTf)_3$-mediated coupling reaction of E-ring and H-ring



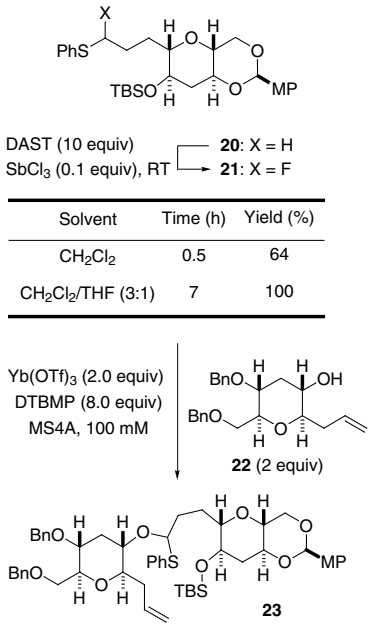
Entry	Solvent	Equiv of **11**	Concentration of **13** (mM)	Temperature	Time (h)	Yield (%)		
						15	**17**	**18**
1	CH_2Cl_2	1.2	50	−30 °C to rt	21	25	33	13
2	CH_3NO_2	1.2	50	−30 to 0 °C	5	—[a]	—	—
3	THF	1.2	50	−80 to 5 °C	6	20 (33)[b]	18	5
4	DME	1.2	50	−70 to 0 °C	7	41	40	16
5	DME	1.2	100	−60 to −10 °C	5	57	26	4
6	DME	2.0	100	−60 to −15 °C	9	79	17	0
7	THF	2.0	100	−80 to 0 °C	6	56	27	0

[a] Complex mixture was obtained.
[b] Starting material **13** was isolated in 40% yield. Yield in parenthesis is based on recovered **13**.



Scheme 2. Mechanistic rationale of formation of **17** and **18**.

sensitive functionalities (Scheme 3). Fluorination of **20** under the same conditions as **12** afforded **21** in only 64% yield, and the *p*-methoxybenzylidene removal was observed. Interestingly, the use of THF as co-solvent dramatically suppressed this acid-catalyzed side reaction to provide **21** as a single isomer in 100% yield. α-Fluorosulfide **21** was then successfully coupled with alcohol **22** (2 equiv) by the action of $Yb(OTf)_3$ in either DME or THF as solvent. A slightly better result was obtained using THF, in which the adduct **23** was produced in 84% yield (a 5:3 diastereomer ratio).[14]



Solvent	Time (h)	Yield (%)
CH_2Cl_2	0.5	64
CH_2Cl_2/THF (3:1)	7	100

Solvent	Temperature	Time (h)	Yield (%)
DME	–60 °C to –20 °C	4	72
THF	–70 °C to –20 °C	5	84

Scheme 3. $Yb(OTf)_3$-mediated coupling reaction of acetal-protected substrate.

In conclusion, we have devised the new reaction to construct *O*,*S*-acetals, important intermediates for the synthesis of polyethers. It is particularly noteworthy that $Yb(OTf)_3$ effected the activation of the stable α-fluorosulfides at low temperatures. The mild, yet powerful nature of the reaction is likely to enable efficient synthesis of the gigantic natural and artificial polyethers. Furthermore, *O*,*S*-acetals have been utilized as acyclic glycosyl donors,[15] thus the method presented should be synthetically useful for the oligosaccharides. Application of the newly developed method to complex substrates such as ciguatoxins is currently under active investigation.

Acknowledgements

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13. The important aspect of the mixed-acetal strategy is that the stereoselective synthesis of the *O*,*S*-acetal is not necessary, because the stereochemical information at the acetal carbon is lost upon radical cyclization conditions (**8** → **9**). See Refs. 8 and 9.
14. General procedure for the coupling reaction: To a solution of sulfide **20** (43 mg, 81 μmol) in CH_2Cl_2/THF (3:1, 1.6 mL) was added DAST (107 μL, 810 μmol) and $SbCl_3$ (1.8 mg, 8.1 μmol) at room temperature. The reaction mixture was stirred for 7 h, then quenched with saturated aqueous $NaHCO_3$, and diluted with EtOAc. The organic layer was washed with brine, dried (Na_2SO_4), concentrated, and purified by flash column chromatography [hexane/EtOAc (50:1) containing 1% Et_3N] to give α-fluorosulfide **21** (48 mg) in 100% yield.
To a suspension of α-fluorosulfide **21** (10 mg, 18 μmol), alcohol **22** (13.3 mg, 36 μmol) and molecular sieves 4A (10 mg) in THF (0.18 mL) at −70 °C was sequentially added DTBMP (30 mg, 144 μmol) and $Yb(OTf)_3$ (22 mg, 36 μmol). The reaction mixture was stirred for 5 h at −70 to −20 °C, then quenched with saturated aqueous $NaHCO_3$, and diluted with EtOAc. The organic layer was washed with brine, dried (Na_2SO_4), concentrated, and purified by flash column chromatography [hexane/EtOAc (20:1) containing 1% Et_3N] to give *O*,*S*-acetal **23** (13.6 mg) in 84% yield.
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