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Tetrahedron Letters
Tetrahedron Letters 45 (2004) 7567–7571

Novel branched ether formation via conjugate reduction of an unsaturated cyanohydrin derivative and its synthetic application to the EF-ring segment of ciguatoxin

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Received 29 July 2004; revised 18 August 2004; accepted 20 August 2004

Abstract—A synthetic method for a branched ether system was developed. The method was based on Lewis-acid-promoted γ-position selective reduction of a γ-alkoxy β,γ-unsaturated α-silyloxy nitrile, prepared through a process including intermolecular hetero-Michael reaction of a 2-butynoate ester derivative with an alcohol. The method was efficiently applied to the synthesis of fused medium-ring ethers involving the EF-ring segment (**2**) of ciguatoxin (**1**).

Since medium-sized cyclic ethers are often seen in potently bioactive natural products,[1] such as ciguatoxin (**1**),[1a,b,e,2–4] they attract significant synthetic attention. So far, many approaches have been studied for their efficient construction.[5] Among these approaches, a ring-closing olefin metathesis reaction (RCM) has currently attracted great interest, because it is a catalytic reaction, which achieves efficient closure of medium cycles under mild conditions and tolerates a wide variety of functional groups in its substrates.[5,6] However, application of RCM to the syntheses of cyclic ethers involves a crucial challenge in the preparation of the substrates for RCM, namely, the stereoselective construction of an acyclic branched ether part in each substrate. Recently, several successful methods based on an alkylation or an aldol reaction of a glycolate ester derivative,[7,8] allyl[9] or hydride[10] addition to an acetal group, an addition reaction of an α-alkoxy carbon radical to a β-alkoxy propenoate ester,[11] or ring cleavage of *C*-glycosides,[12] have been developed to solve the challenge. Nevertheless, the number of methods is insufficient to meet the requirements for the synthesis of varied and complex cyclic ethers. In this context, we have explored new methods for construction of the branched ether system.[12] Here, a new entry of the methods based on Lewis-acid-promoted γ-position selective reduction of a γ-alkoxy β,γ-unsaturated α-silyloxy nitrile group and its application to the synthesis of fused medium-ring ethers involving the EF-ring segment (**2**) of ciguatoxin (**1**) are described (Fig. 1).

Our general synthetic strategy for a fused-bicyclic ether system involving medium rings, shown in Scheme 1, was based on the following four processes: (i) construction of the medium-membered ether ring of **4** by RCM of precursor **5** using Grubbs' method;[6,13] (ii) introduction of a hydroxy group to the β-position of the branched ether part of **6**; (iii) reduction of the 3-alkoxy-2-butenoate part of **7** and (iv) hetero-Michael reaction of 2-butynoate ester **9** with alcohol **8** according to Paintner's procedure.[14] The success of this synthesis strongly relied on the achievement of the third process, which would construct the branched ether system.[15] Therefore, a reductive transformation reaction shown in Scheme 2 was newly designed. We expected that γ-alkoxy β,γ-unsaturated α-silyloxy nitrile **10** would be activated by an appropriate Lewis acid to generate oxonium ion **11**, which would be selectively reduced at the γ-position into γ-alkoxy α,β-unsaturated nitrile **12** by a proper reducing agent. The nitrile group would be available for further synthesis toward **5**.

Keywords: Fused medium-ring ether; Ciguatoxin; Branched ether synthesis; Hetero-Michael addition.
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doi:10.1016/j.tetlet.2004.08.117

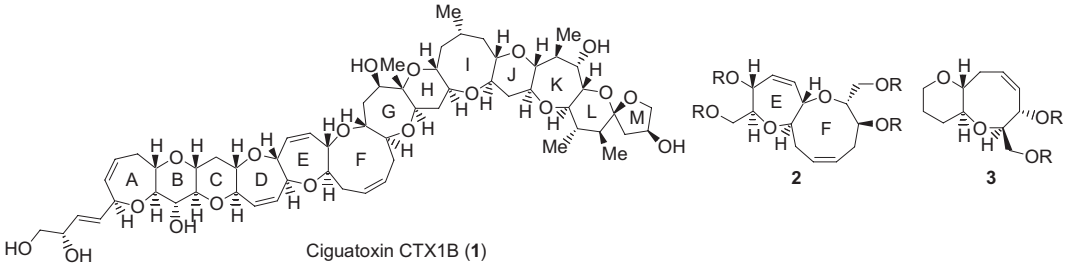
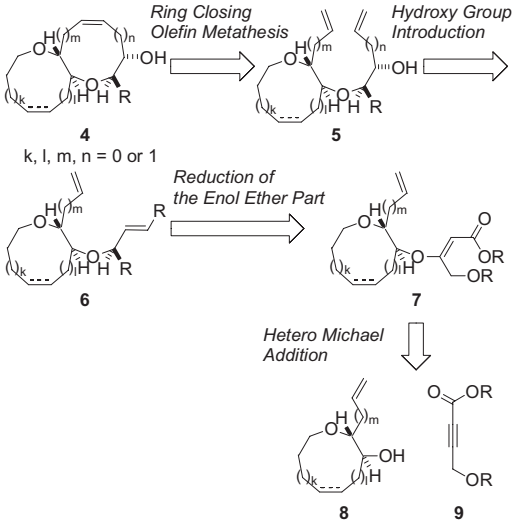
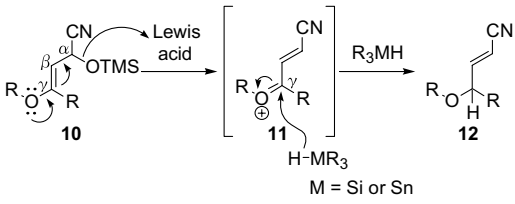


Figure 1.



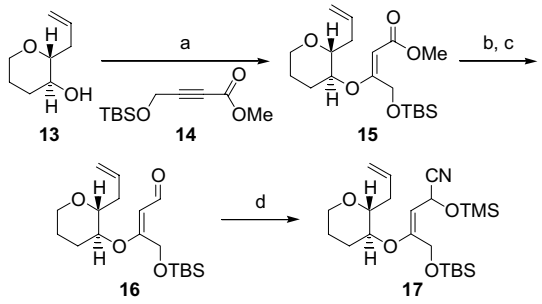
Scheme 1. Synthetic plan for fused-bicyclic ether **4**.



Scheme 2. Lewis-acid-promoted γ-position selective reduction of a γ-alkoxy β,γ-unsaturated α-silyloxy nitrile system.

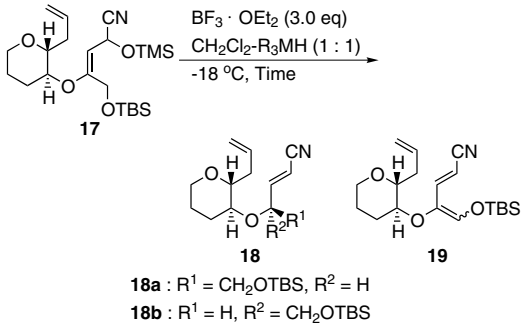
First, we planned to synthesize fused 6/8 cyclic ether **3**, which has a side chain and a hydroxyl group with proper stereochemistry available for further construction of a *trans*-fused ether ring, from **13**[16] and **14** according to the above strategy. Reduction precursor **17** was synthesized according to Scheme 3. Hetero-Michael addition of **13** to butynoate **14** in the presence of Me_3P afforded **15** in 74% yield and gave **13** in 20% recovery.[17] The ester **15** was converted to aldehyde **16** through reduction and oxidation reactions in 88% yield. Treatment of **16** with TMSCN (2.5 equiv) in the presence of Me_3Al in benzene at ambient temperature gave **17** as a 1:1 mixture of diastereomers in 71% yield.

Next, reduction of **17** with several organometallic hydride reagents was examined (Table 1). All reactions were carried out in a 1:1 (v/v) mixture of a hydride reagent and CH_2Cl_2 in the presence of $BF_3{\cdot}OEt_2$ (3.0 equiv)



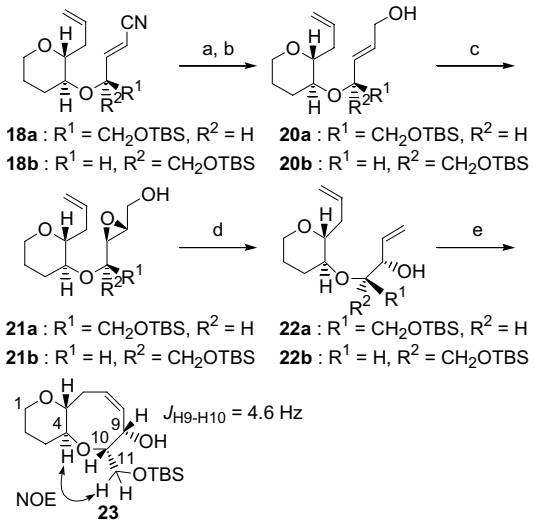
Scheme 3. Preparation of reduction precursor **17**. Reagents and conditions: (a) PMe_3 (1.0 equiv), **14** (2.8 equiv), CH_2Cl_2–THF, 25 °C, 24 h, 74% (only *E*), 20% recovery of **13**; (b) DIBAH (4.0 equiv), CH_2Cl_2, −78 °C, 10 min, ~100%; (c) TPAP (0.1 equiv), NMO (2.0 equiv), MS 4 Å, CH_2Cl_2, 24 °C, 50 min, 88%; (d) Me_3Al (1.1 equiv), TMSCN (2.5 equiv), benzene, 24 °C, 1 h, 71%.

Table 1. $BF_3{\cdot}OEt_2$ promoted reduction of **17** with several reducing reagents



Entry	R_3MH	Time (min)	Yield (%)	**18a**:**18b**:**19**
1	Et_3SiH	17	71	1.9:3.8:1.0
2	Et_2MeSiH	10	65	1.8:3.9:1.0
2	$EtMe_2SiH$	10	74	1.4:3.5:1.0
4	Me_2PhSiH	10	61	2.0:4.2:1.0
5	Bu_3SnH	10	64	1.0:1.3:0

at −18 °C.[18] All organosilanes afforded a mixture of nitriles **18a**, **18b**, and **19** in 61–74% yield (entries 1–4). It was noted that the ratio of **18a** to **18b** increased with increasing bulkiness of the organosilane. On the other hand, the reaction with Bu_3SnH gave the best result, in which only the desired nitriles **18a** and **18b** were produced as an inseparable 1.0:1.3 mixture in 64% yield (entry 5). The stereochemistry at the newly formed stereocenters of **18a** and **18b** was determined after trans-



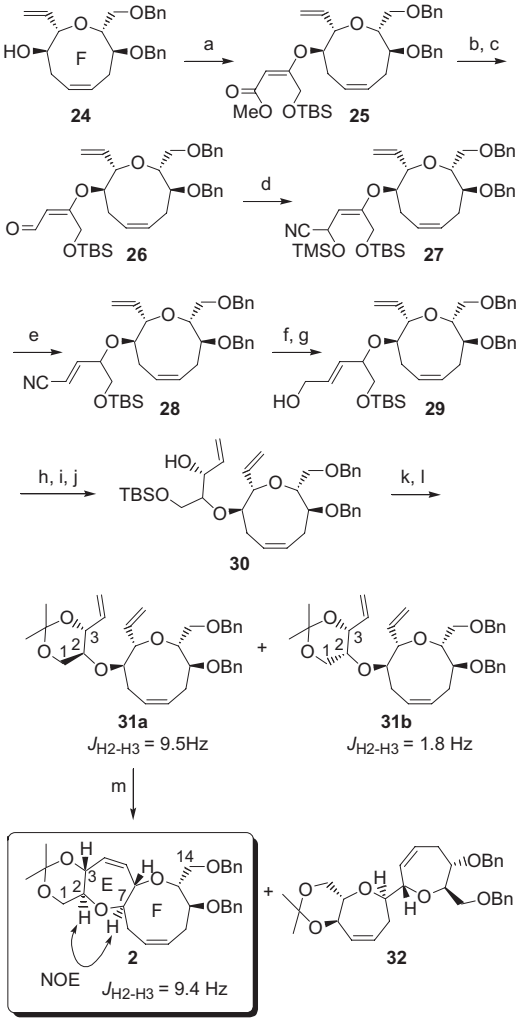
Scheme 4. Synthesis of bicyclic ether **23**. Reagents and conditions: (a) DIBAH (2.5 equiv), CH_2Cl_2, −78 °C, 10 min, 68%; (b) DIBAH (3.0 equiv), CH_2Cl_2, −78 °C, 8 min, ~100%; (c) D-(−)-DET (0.8 equiv), $Ti(O^iPr)_4$ (0.7 equiv), TBHP (5.0 equiv), MS 4 Å, CH_2Cl_2, −40 °C, 30 min → −25 °C, 24 h, ~100%; (d) Ph_3P (5.0 equiv), imidazole (5.0 equiv), I_2 (4.0 equiv), THF, 25 °C, 45 min, 61%; (e) [{CH_2-(Mes)N}$_2$C](Cl)$_2$(PCy_3)Ru=CHPh (10 mol%), CH_2Cl_2 (5 mM), reflux, 6 h, 44%.

formation of **18b** into bicyclic ether **23** (vide infra). Thus, efficient conditions for the γ-selective reduction of α-silyloxy nitrile **17** were found.

Synthesis of a 6/8 bicyclic system from **18a** and **18b** is shown in Scheme 4. A ca. 1:2 mixture of **18a** and **18b** was converted to a mixture of allyl alcohols **20a** and **20b** (68%) by repeated reduction with DIBAH. The allyl alcohols were subjected to Katsuki–Sharpless asymmetric epoxidation[19] using (−)-DET to produce a mixture of epoxides **21a** and **21b** (~100%), which was treated with PPh_3 and I_2 in the presence of imidazole at ambient temperature to give allyl alcohols **22a** and **22b** (61%) as a 1:2 mixture.[20,21] Ring closure of dienes **22a** and **22b** in refluxing CH_2Cl_2 by Grubbs' second-generation catalyst[22] gave a mixture of products, in which only **23** was isolated as a bicyclic product (44%), and the desired **3** was not detected.[23] Stereochemistry of **23** was confirmed by the presence of NOE between H4 and H11 as well as the small *J* value between H9 and H10 (4.6 Hz). From the fact that the 1:2 ratio of the diastereomers was maintained throughout the transformation process from **18** to **22**, and that the yield of **23** (44%) was apparently higher than the ideal yield (33%) of the cyclization product from minor diastereomer **22a**, it was concluded that **23** was produced from **22b** and originated from **18b**.

The results from the final RCM step suggested that the vinyl groups of **22a** were apart from each other in the stable conformation of **22a**, and such orientation of the vinyl groups was inappropriate for the cyclization of **22a**. Therefore, we decided to prepare a *bicyclic* RCM precursor, of which the vinyl group would be placed in close proximity to each other, for successful ring closure in the synthesis of a *trans*-fused-bicyclic ether system.

Then, we examined the synthesis of the EF-ring segment (**2**) of ciugatoxin (**1**) according to the above considerations (Scheme 5). Hetero-Michael addition of the F-ring part **24**[24] to 2-butynoate ester **14** gave **25** in good yield (90%),[14] which was converted to α-silyloxy nitrile **27** through reduction, oxidation, and addition of TMSCN.



Scheme 5. Synthesis of the EF-ring segment (**2**) of ciguatoxin CTX1B (**1**). Reagents and conditions: (a) PMe_3 (1.5 equiv), **14** (3.0 equiv), CH_2Cl_2, 0 → 24 °C, 1 h, 90% (only *E*); (b) DIBAH (4.0 equiv), CH_2Cl_2, −78 °C, 10 min, 99%; (c) TPAP (0.1 equiv), NMO (2.0 equiv), MS 4 Å, CH_2Cl_2, 24 °C, 1.5 h, 75%; (d) Me_3Al (1.1 equiv), TMSCN (2.5 equiv), benzene, 24 °C, 1 h, 79%; (e) $BF_3{\cdot}OEt_2$ (3.0 equiv), CH_2Cl_2–Bu_3SnH (1:1), −18 °C, 15 min, 55%, 18% recovery of **27**; (f) DIBAH (2.5 equiv), CH_2Cl_2, −78 °C, 10 min; (g) DIBAH (6.0 equiv), CH_2Cl_2, −78 °C, 20 min, 72% for two steps; (h) L-(+)-DET (1.5 equiv), $Ti(O^iPr)_4$ (1.3 equiv), TBHP (10 equiv), MS 4 Å, CH_2Cl_2, −40 °C, 30 min → −25 °C, 26 h; (i) Ph_3P (5.0 equiv), imidazole (5.0 equiv), I_2 (4.0 equiv), THF, 25 °C, 35 min; (j) Zn (7.0 equiv), EtOH–satd NH_4Claq (40:1), 25 °C, 2.5 h, 68% for three steps; (k) TBAF (1.5 equiv), THF, 25 °C, 11.5 h, 68%; (l) 2,2-dimethoxypropane (4.0 equiv), CSA (0.5 equiv), CH_2Cl_2, 24 °C, 3 h then acetone (5.0 equiv), 11.5 h, **31a**: 50%, **31b**: 46%; (m) $(Cy_3P)_2Cl_2Ru$=CHPh (25 mol%), CH_2Cl_2 (3 mM), 24 °C, 15 h, **31a**:**2**:**32** = 1:1:0.5; $(Cy_3P)_2Cl_2Ru$=CHPh (30 mol%), CH_2Cl_2 (3 mM), 24 °C, 24 h, **2**: 67%, **32**: 24%, after two cycles.

The reduction of **27** with Bu_3SnH in CH_2Cl_2 in the presence of $BF_3{\cdot}OEt_2$ (3 equiv) at −18 °C smoothly produced nitrile **28** as a 1:1 mixture of diastereomers in 55% yield and gave **27** in 18% recovery. Conversion of nitrile **28** to allyl alcohol **29** followed by a three-step transformation [(i) Katsuki–Sharpless asymmetric epoxidation[19] using (+)-DET; (ii) iodation of the hydroxyl group[20] and (iii) reduction of the resulting epoxy iodide with Zn] gave the corresponding allyl alcohol **30** as a 1:1 mixture of diastereomers in 68% yield. In order to facilitate the closure of the *trans*-fused medium ring by RCM and to confirm the stereochemistry of each diastereomer, acetonides **31a** and **31b** were synthesized from **30** through removal of the TBS group followed by protection of the resulting diol. Diastereomers **31a** and **31b** were easily separated by silica gel column chromatography, and the stereochemistry of each compound was determined by the *J* value between H2 and H3. RCM[6,13] of **31a** with Grubbs' first-generation catalyst in CH_2Cl_2 at ambient temperature successfully produced the desired *trans*-fused EF-ring segment **2** of ciguatoxin (**1**) in 67% yield along with **32** in 24% yield.[25] The stereochemistry of **2** was confirmed by the presence of NOE between H2 and H7 as well as the large *J* value between H2 and H3 (9.4 Hz).[26]

Thus, we have developed a novel branched ether formation reaction based on Lewis-acid-promoted γ-position selective reduction of a γ-alkoxy β,γ-unsaturated α-silyloxy nitrile group. The reaction has been employed for the construction of fused-bicyclic ether **23** and the EF-ring segment (**2**) of ciguatoxin (**1**).

Acknowledgements

We thank Mr. Kenji Watanabe and Dr. Eri Fukushi (GC–MS & NMR Laboratory, Graduate School of Agriculture, Hokkaido University) for the measurements of mass spectra. This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology of Japanese Government.

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15. Several attempts to reduce selectively the α,β-unsaturated ester part of **15** were unsuccessful.
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17. Hetero-Michael addition of **13** to butynoate **14** with a catalytic amount of Me_3P according to Paintner's procedure[14] often stopped without completion. The incomplete reaction was due to the oligomerization of **14**. A stoichiometric amount of Me_3P and excess **14** (2.8 equiv) were required to accelerate the reaction rate and to improve the yield.
18. When TMSOTf was used in stead of $BF_3{\cdot}OEt_2$, complex products were obtained. On the other hand, Me_3Al was ineffective in activating the substrate.

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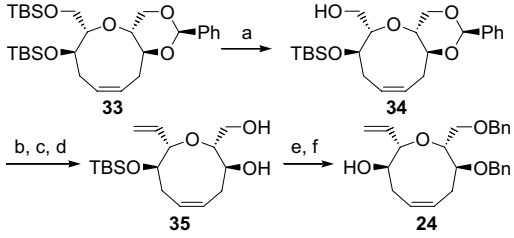
23. In the RCM reaction, **22a** was not recovered, and an oligomer that would be resulted from **22a** was detected.
24. The F-ring derivative **24** could be synthesize in six steps from the reported compound **33**.[12b]



Reagents and conditions: (a) H_3O^+, 68%; (b) Swern oxid.; (c) $Ph_3P{=}CH_2$; (d) $HSCH_2CH_2SH$, $NaHCO_3$, $Zn(OTf)_2$, 58% for three steps; (e) NaH, BnBr, TBAI; (f) TBAF, ~100% for two steps.

25. Since the RCM reaction of **31a** often stopped without completion, this step was repeated once in order to consume **31a** completely. Optimization of the step is currently under way.
26. Spectral data of **2**: a colorless oil; $[\alpha]_D^{23}$ +13.0 (*c* 0.20, $CHCl_3$); ^1H NMR (300 MHz, $(CD_3)_2C{=}O$, $CHD_2C(=O)$-CD_3 as 2.04 ppm), δ 7.34–7.24 (10H, m, Bn), 6.00 (1H, dt, J = 12.4, 2.6 Hz, H4 or H5), 5.78–5.67 (2H, m, H9, H10), 5.40 (1H, dt, J = 12.4, 2.6 Hz, H4 or H5), 4.68 (1H, d, J = 11.6 Hz, Bn), 4.49 (2H, s, Bn), 4.41 (1H, d, J = 11.6 Hz, Bn), 4.30 (1H, br dqn, J = 9.4, 2.6 Hz, H3), 3.88–3.83 (1H, m, H6), 3.72 (1H, dd, J = 11.3, 5.7 Hz, H1eq), 3.70–3.61 (3H, m, H12, H14a,b), 3.58–3.50 (1H, m, H7), 3.55 (1H, dd, J = 11.3, 9.4 Hz, H1ax), 3.29 (1H, ddd, J = 8.5, 5.7, 2.6 Hz, H13), 3.18 (1H, td, J = 9.4, 5.7 Hz, H2), 2.89–2.78 (1H, m, H8), 2.66–2.58 (1H, m, H11), 2.39 (1H, m, H11), 2.07–1.98 (1H, m, H8), 1.42 (3H, s, Me), 1.28 (3H, s, Me); IR (film) ν_{max} 3087, 3063, 3027, 2991, 2922, 2855, 1496, 1454, 1372, 1336, 1311, 1292, 1267, 1221, 1200, 1100, 1027, 988, 945, 893, 866, 779, 767, 735, 697, 680 cm^{-1}; LR-FDMS, *m/z* 506 (22.4%, $[M]^+$), 491 (47.9%, $[M-Me]^+$), 91 (bp); HR-FDMS, calcd for $C_{31}H_{38}O_6$ $[M]^+$: 506.2669, found: 506.2650.