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Convergent synthesis of the EFGH ring fragment of ciguatoxin CTX3C

Hiroto Imai, Hisatoshi Uehara, Masayuki Inoue, Hiroki Oguri, Tohru Oishi and Masahiro Hirama*

Department of Chemistry, Graduate School of Science, Tohoku University, and CREST, Japan Science and Technology Corporation (JST), Sendai 980-8578, Japan

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Abstract—A stereoselective synthesis of the EFGH ring fragment of ciguatoxin CTX3C has been achieved through: (i) selective cleavage of a dioxepane acetal C–O bond; (ii) radical cyclization to form the oxepane G ring; and (iii) chemoselective ring-closing metathesis of a triene yielding the hexahydrooxonin F ring.

Ciguatoxin (**1**)[1] and CTX3C[2] (**2**) are the principal toxins that cause ciguatera seafood poisoning prevalent in the tropics and subtropics (Scheme 1).[3] Their structural complexity and potent activity for the voltage-sensitive sodium channel have attracted great attention among synthetic chemists.[4–6] During the course of our synthetic studies directed toward **2**, we have achieved the synthesis of the ABCDE ring **3** based on an alkylation/ring-closing metathesis (RCM) strategy,[4f] and the HIJKLM ring **4** based on a RCM featuring an intramolecular carbonyl olefination using a low-valent titanium complex.[4e] With these compounds in hand, development of an efficient coupling strategy which simultaneously constructs the FG ring system was an imperative prerequisite to the total synthesis of CTX3C. To this end the EFGH ring fragment **5** was selected as a prime synthetic target.

Recently, Sasaki and co-workers have reported a synthesis of the FGH ring system of ciguatoxins via cleavage of a dioxane acetal, stereoselective intramolecular radical cyclization to construct the oxepane ring G,[7] and closure of the hexahydrooxonin ring F by a RCM reaction.[8] Although this strategy seems to be quite applicable to our synthetic program on CTX3C, unification of the large and complex fragments (**3**+**4**→**2**) would necessitate carefully controlled conditions compatible with the sensitive functionalities such as the allylic ethers (**3**) and the ketal structure (**4**). In the event, Lewis acid-promoted cleavage of dioxane acetal **8** that neighbors an unsaturated eight-membered ring E was found to be problematic, and it was therefore necessary to develop an alternative approach. In this report, we present critical modifications to overcome this problem, and the assembly of the EFGH ring fragment **5** which has been achieved in a highly convergent manner.

Condensation of diol **6**[4f] with aldehyde **7**[4e] using $Sc(OTf)_3$ as the catalyst[8,9] afforded the dioxane acetal **8** as a single isomer in 93% yield (Scheme 2). The desired *O*,*S*-acetal **9** was obtained in only a 6% yield by treatment of **8** with Et_2AlSPh.[8,10] In addition, the dithioacetals, **10** (2%) and **11** (8%), as well as the debenzylated products, **12** (11%) and **13** (16%), were isolated as by-products. Since seven-membered ring acetals are generally more prone to undergo hydrolysis than the six-membered counterparts, the dioxepane acetal **16** was expected to react with Lewis acids more readily to give an *O*,*S*-acetal (Scheme 3).[11] To test this idea, the E ring diol **6** was selectively tosylated and treated with sodium cyanide to give nitrile **14**, which was reduced sequentially with DIBAL-H and then with sodium borohydride to generate the diol **15**, the one carbon homologue of **6**. Subsequent coupling of **15** with **7** by the action of $Sc(OTf)_3$ afforded dioxepane acetal **16** as a C11 epimeric mixture (87%, H_β:H_α = 2.8:1). The stereochemistry of the major β-epimer **16** was confirmed by NOE experiments. Having successfully prepared the dioxepane **16**, acetal cleavage was then investigated. Treatment of **16** with excess Et_2AlSPh afforded *O*,*S*-acetal **17** together with the debenzylated product **18** in a combined yield of 76%.

Keywords: ring-closing metathesis; acetal cleavage; radical reaction; ciguatoxin; polyethers; stereocontrolled synthesis.

* Corresponding author. Fax: +81-22-217-6566; e-mail: hirama@ykbsc.chem.tohoku.ac.jp

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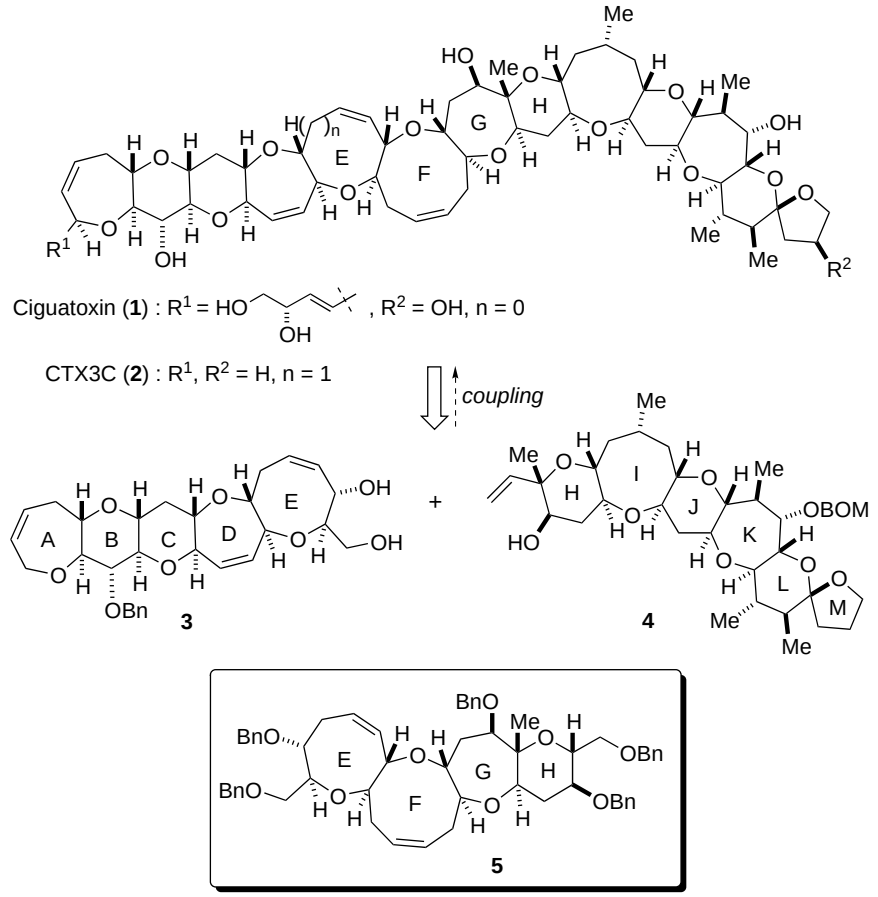
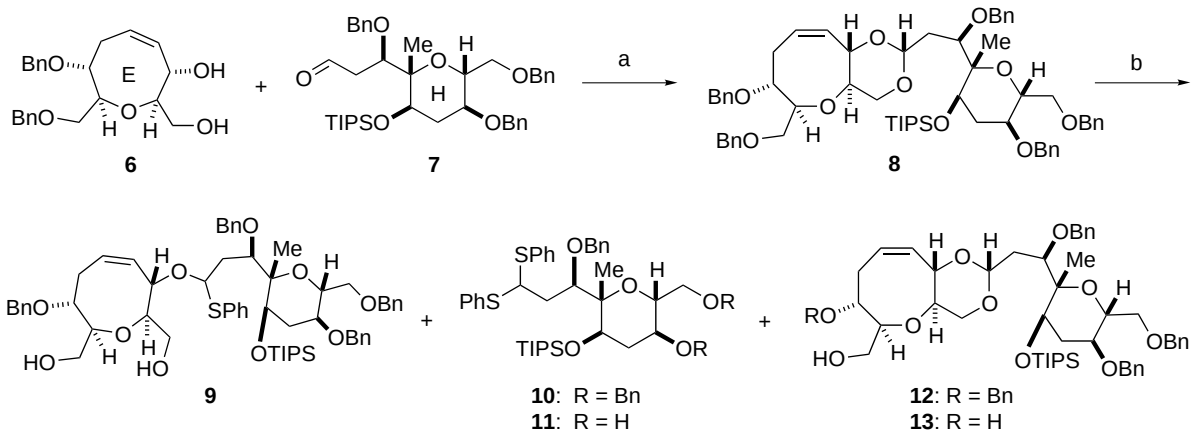


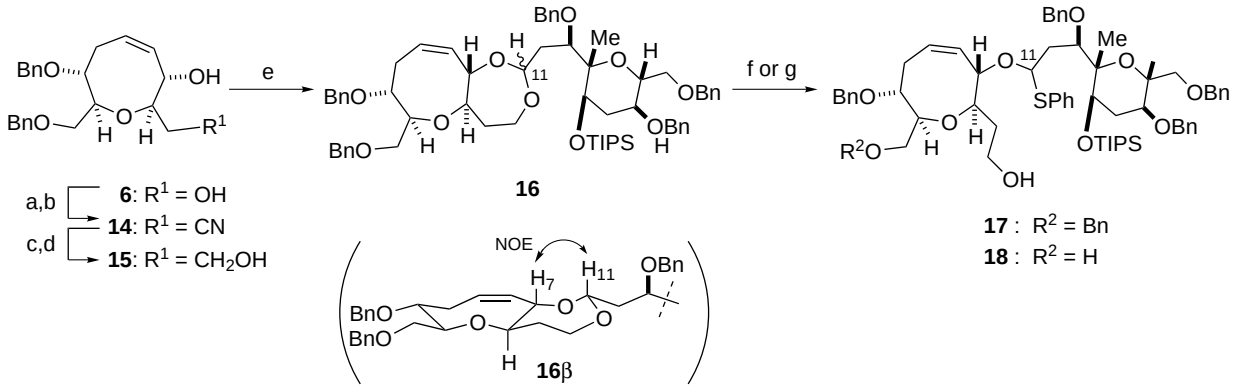
Scheme 1. Development of a strategy to couple **3** and **4** for the total synthesis of CTX3C.



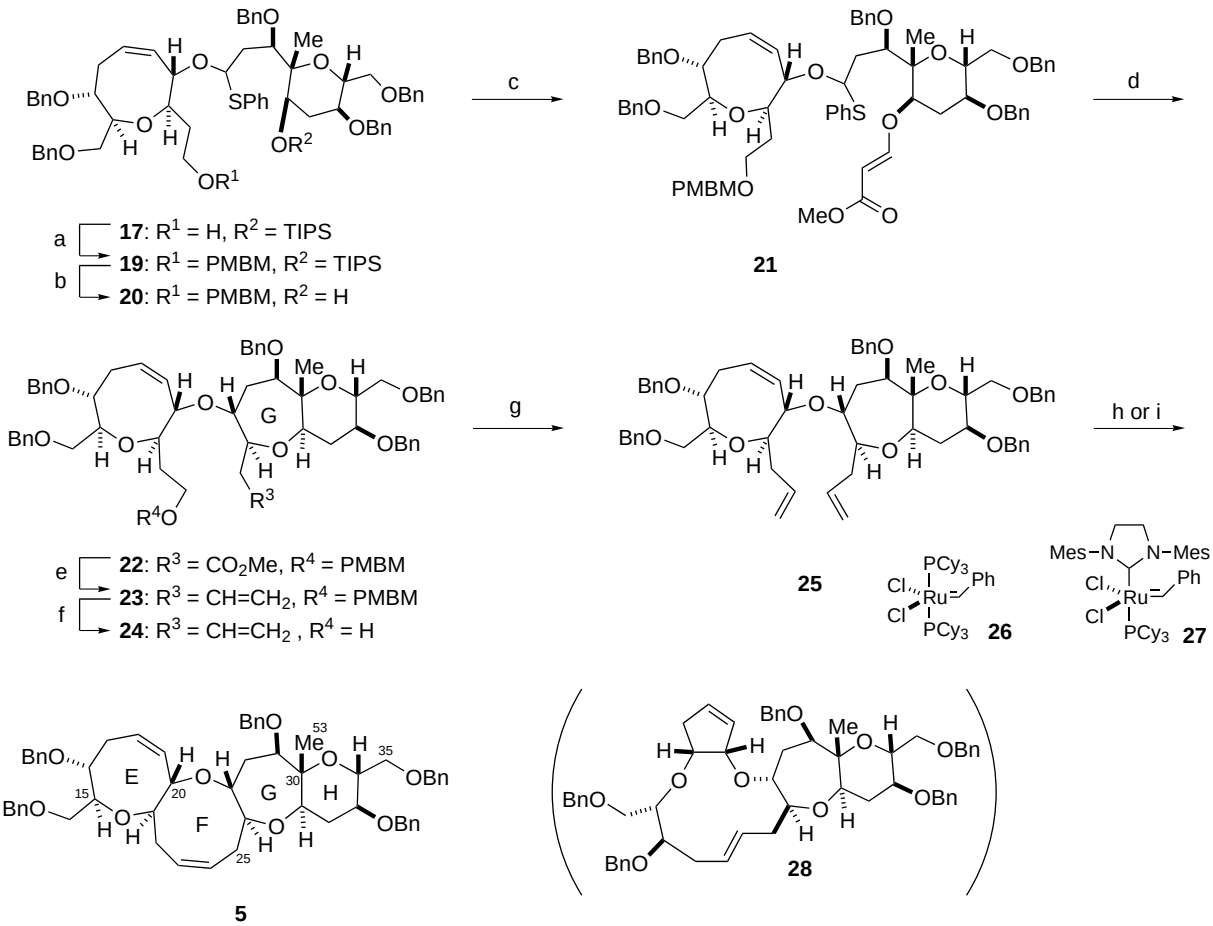
Scheme 2. *Reagents and conditions*: (a) **7** (1.4 equiv.), $Sc(OTf)_3$, benzene, 93%; (b) Et_2AlSPh (5 equiv.), −5°C, CH_2Cl_2–hexane (1:2), **9**: 6, **10**: 2, **11**: 8, **12**: 11, **13**: 16%, recovered **8**: 18%.

After considerable experimentation to suppress the concomitant debenzylation, we found that a reagent combination of Me_3SiSPh and Me_3SiOTf[12] was superior, and solely generated **17** as a single diastereomer[13] in 87% yield.[14]

Construction of the FG ring is summarized in Scheme 4. Protection of the primary alcohol of **17** as a *p*-methoxybenzyloxymethyl (PMBM) ether, removal of the TIPS group, and then treatment of **20** with methyl propiolate and *N*-methylmorpholine provided β-alkoxyacrylate **21** in 97% overall yield (3 steps). For closure of the G ring, a solution of **21** in toluene was treated with AIBN and *n*-Bu_3SnH at 80°C, producing the oxepane **22** selectively with the desired stereochemistry.[7,8] DIBAL-H reduction of **22** to an aldehyde and Wittig methylenation then gave olefin **23** in 86% yield (2 steps). Removal of the PMBM group afforded alcohol **24**, which was oxidized and also subjected to a Wittig methylenation to furnish triene **25**. The regio-



Scheme 3. *Reagents and conditions*: (a) TsCl, pyridine, 98%; (b) NaCN, DMSO, 50°C, 80%; (c) DIBAL-H, CH_2Cl_2, −78°C, 85%; (d) $NaBH_4$, MeOH, −60 to −30°C, 95%; (e) **7** (1.3 equiv.), $Sc(OTf)_3$, benzene, 87% (β:α = 2.8:1); (f) using **16**β, Et_2AlSPh (5 equiv.), −5°C, CH_2Cl_2–hexane (1:2), **17**: 24%, **18**: 52%, recovered **16**: 23%; (g) using **16** (β:α = 3:1), (i) Me_3SiSPh, Me_3SiOTf, CH_2Cl_2, −50 to 0°C; (ii) K_2CO_3, MeOH, rt, **17**: 87%.



Scheme 4. *Reagents and conditions*: (a) PMBMCl, *i*-Pr_2NEt, *n*-Bu_4NBr, $(CH_2Cl)_2$, 40°C; (b) TBAF, THF, 35°C; (c) methyl propiolate, *N*-methylmorpholine, CH_2Cl_2, 97% (three steps); (d) *n*-Bu_3SnH, AIBN, toluene, 80°C; (e) (i) DIBAL-H, CH_2Cl_2, −100 to 80°C; (ii) NaHMDS, Ph_3PCH_3Br, THF, 0°C, 86% (three steps); (f) TMSBr, CH_2Cl_2, −60 to −20°C, 78%; (g) (i) SO_3·pyr, Et_3N, CH_2Cl_2–DMSO, 0°C; (ii) NaHMDS, Ph_3PCH_3Br, THF, 0°C, 75% (two steps); (h) **26** (30 mol%), CH_2Cl_2, 40°C, 8 h, **5**: 77%; (i) **27** (15 mol%), $CDCl_3$, 40°C, 1.5 days, **5**: 35, **28**: 14%.

and chemoselective RCM reaction of the triene **25** was the final and most challenging step in this synthesis.[15,16] Fortunately, the RCM reaction of **25** using Grubbs catalyst **26**[17] at 40°C in CH_2Cl_2 provided the targeted EFGH ring fragment **5**[18] in 77% yield without touching the disubstituted olefin in the E ring.[17] However, use of the more reactive Grubbs catalyst **27**[19] resulted in a decreased yield of **5** due to E ring opening and subse-

quent RCM leading to by-product **28**. This successful RCM reaction is especially important for the total synthesis of ciguatoxins, where the multiple olefinic functionalities are potential problems. The ^{1}H NMR signals of the hexahydrooxonin ring of **5** were severely broadened at room temperature due to relatively slow conformational changes, as has been observed for ciguatoxin,[1a] CTX3C,[2] and other model compounds.[8,20,21]

To conclude, we have succeeded in an efficient assembly of the central EFGH ring system (**5**) of CTX3C (**2**) through the opening of a seven-membered acetal (**16**→**17**) by the action of Me_3SiSPh and Me_3SiOTf, and a chemoselective ring-closing metathesis of the triene (**25**→**5**) by carefully selected conditions. The viability of this convergent strategy to the total synthesis of CTX3C is currently under active investigation and will be reported in due course.

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18. Physical data for **5**. $[\alpha]_D^{22}$ −73.6 (*c* 0.62, $CHCl_3$); IR (film): 3063, 2924, 1496, 1365, 1206, 1028 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, −20°C): δ 1.24 (3H, s, H53), 1.66 (1H, q, *J*=11.5 Hz, H32), 2.00–2.12 (2H, m, H25, 28), 2.19–2.27 (2H, m, H22, 28), 2.38 (1H, dt, *J*=12.0, 4.5 Hz, H32), 2.38–2.45 (2H, m, H17×2), 2.77–2.86 (2H, m, H22, 25), 3.28 (1H, dd, *J*=11.0, 4.5 Hz, H31), 3.27–3.32 (1H, m, H27), 3.42 (1H, dd, *J*=10.0, 6.5 Hz, H14), 3.46–3.70 (10H, m, H14, 15, 16, 21, 26, 29, 33, 34, 35×2), 3.85 (1H, dd, *J*=8.0, 6.0 Hz, H20), 4.33 (1H, d, *J*=11.0 Hz, CH_2Ph), 4.39 (1H, d, *J*=11.5 Hz, CH_2Ph), 4.54 (2H, s, CH_2Ph), 4.57 (1H, d, *J*=11.5 Hz, CH_2Ph), 4.596 (1H, d, *J*=12.0 Hz, CH_2Ph), 4.602 (1H, d, *J*=11.0 Hz, CH_2Ph), 4.61 (1H, d, *J*=12.0 Hz, CH_2Ph), 4.62 (1H, d, *J*=11.0 Hz, CH_2Ph), 4.73 (1H, d, *J*=12.0 Hz, CH_2Ph), 5.60–5.69 (1H, m, H18), 5.74 (1H, dt, *J*=11.0, 5.5 Hz, H24), 5.79 (1H, dd, *J*=11.5, 6.0 Hz, H19), 5.82 (1H, dt, *J*=11.0, 5.0 Hz, H23), 7.22–7.35 (25H, m, Ph); MALDI–TOF MS: calcd for $C_{58}H_{66}NaO_9$ [M+Na$^+$] 929.46; Found 929.48.
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21. Only a single set of ^{1}H NMR signals was observed at −20°C in pyridine, which suggested that **5** existed mostly as one conformer. This conformational behavior is more similar to the natural products (**1** and **2**)[1,2] than the model compounds, in which two conformers were clearly observed.[20] The detailed NMR analysis will be published elsewhere.