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SYNTHESIS OF THE E RING SEGMENT OF CIGUATOXIN CTX3C VIA THE NEGISHI COUPLING OF CYCLIC KETENE ACETAL TRIFLATES

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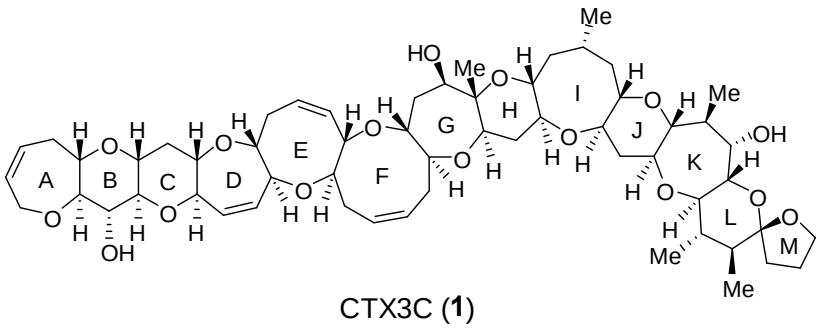
Dedicated to Professor Ei-ichi Negishi on the occasion of his 77th birthday.

Abstract – Stereocontrolled synthesis of the E ring segment of ciguatoxin CTX3C was performed via the Negishi coupling of cyclic ketene acetal triflates. Transformation of 8-membered lactones to the corresponding ketene acetal triflates was found to be affected by the protective groups of the substrates.

Ciguatoxin CTX3C (**1**),[1] isolated from cultured dinoflagellate *Gambierdiscus toxicus*, is a causative toxin of "ciguatera" seafood poisoning (Figure 1).[2] The unique structural features and potent neurotoxicity of this molecule have attracted significant attention of synthetic chemists.[3,4] Herein, we wish to describe a stereocontrolled synthesis of the E ring segment via the Negishi coupling of a cyclic ketene acetal triflate as a part of the synthetic study of **1**.

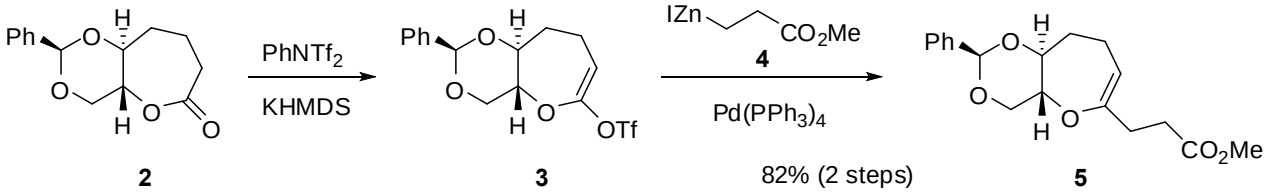


CTX3C (**1**)

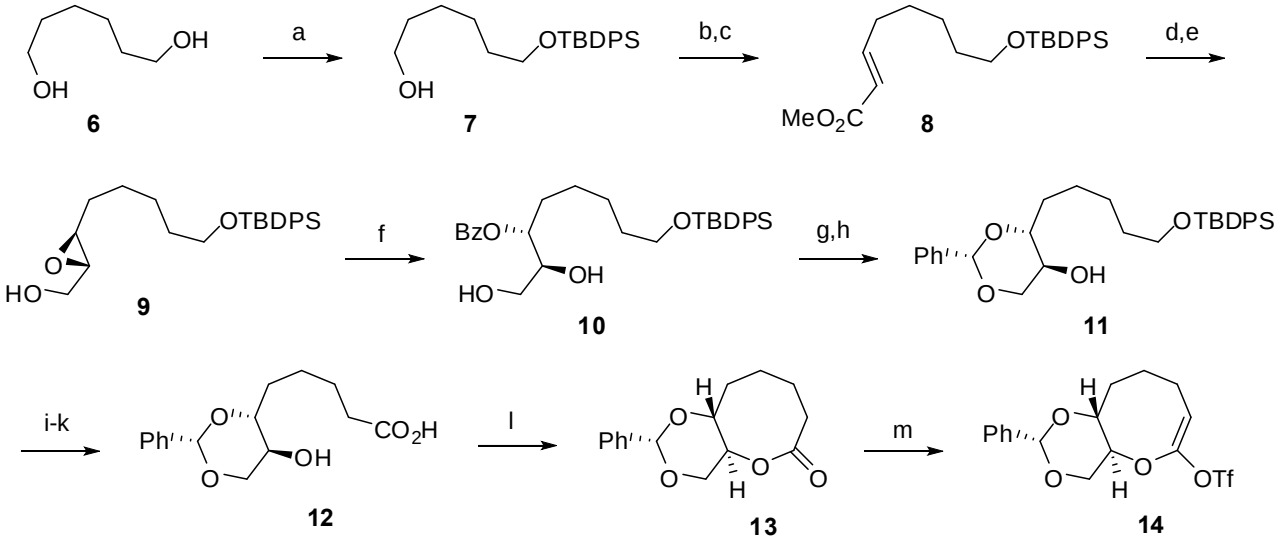
Figure 1. Structure of ciguatoxin CTX3C (**1**)

Previously, we reported the synthesis of cyclic ethers via the Negishi coupling[5] of cyclic ketene acetal triflates prepared from the corresponding lactone and $PhNTf_2$/KHMDS[6] as shown in Scheme 1. Thus, the reaction of the ketene acetal triflate **3**, prepared from ε-lactone **2** with $PhNTf_2$/KHMDS, with zinc

homoenolate **4** in the presence of $Pd(PPh_3)_4$ provided 7-membered cyclic enol ether **5** in 83% yield for the two steps.[7] The reaction was successfully applied to the synthesis of the DE and GH ring segments of gambierol and the C ring of brevetoxin B.[7,8] Encouraged by these results, we attempted to apply this methodology to the synthesis of E ring segment of CTX3C (**1**).



Scheme 1



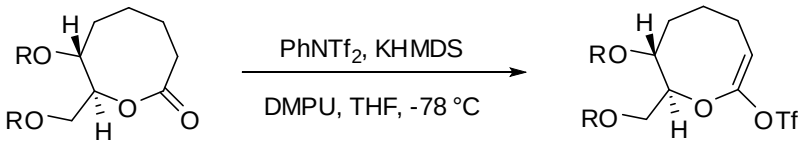
Scheme 2. Reagents and conditions: (a) TBDPSCl, imidazole, CH_2Cl_2, rt; (b) SO_3·py, DMSO, Et_3N, CH_2Cl_2, 0 ºC to rt; (c) $Ph_3P{=}CHCO_2Me$, benzene, rt; (d) DIBAL-H, CH_2Cl_2, -78 ºC; (e) (+)-DET, $Ti(O^iPr)_4$, TBHP, MS4Å. CH_2Cl_2, -30 ºC, 59% (5 steps); (f) $PhCO_2H$, $Ti(O^iPr)_4$, CH_2Cl_2, rt; (g) K_2CO_3, MeOH, rt; (h) $PhCH(OMe)_2$, CSA, CH_2Cl_2, rt, 70% (3 steps); (i) TBAF, THF, rt; (j) TEMPO, $PhI(OAc)_2$, CH_2Cl_2, rt; (k) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, ^tBuOH, H_2O; (l) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, rt, then DMAP, benzene, reflux, 35% (4 steps); (m) $PhNTf_2$, KHMDS, DMPU, THF, -78 ºC, trace.

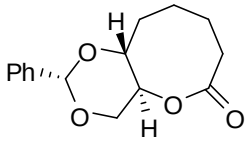
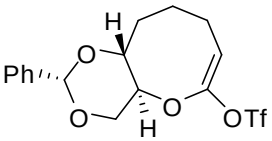
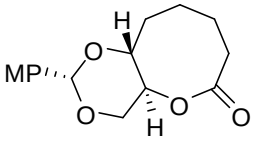
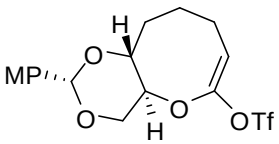
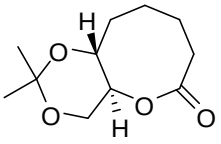
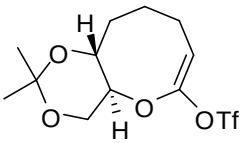
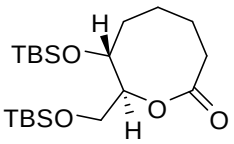
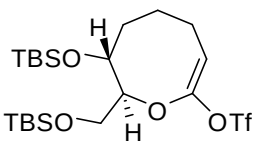
The synthesis of the 8-membered lactone **13** was prepared according to the reported procedure.[9] Protection of 1,6-hexanediol **6** with TBDPSCl/imidazole gave alcohol **7** (Scheme 2). Oxidation of **7** with SO_3·py/DMSO/Et_3N followed by Wittig reaction of the resulting aldehyde with $Ph_3P{=}CHCO_2Me$ afforded α,β-unsaturated ester **8**. Reduction of **8** with DIBAL-H gave the corresponding allylic alcohol, which was subjected to Sharpless asymmetric epoxidation to furnish epoxy alcohol **9** in 59% overall yield. Treatment of **9** with benzoic acid and $Ti(O^iPr)_4$ afforded the benzoate **10**,[10] which was treated with K_2CO_3 in MeOH, and the resulting triol was protected with $PhCH(OMe)_2$/CSA to give the benzylidene acetal **11**

in 70% overall yield. Removal of the TBDPS protection of **11** using TBAF, followed by stepwise oxidation with TEMPO and $NaClO_2$ provided carboxylic acid **12**. Lactonizaton of **12** under Yamaguchi conditions provided **13** in 35% overall yield.[11] The lactone **13** obtained was then treated with $PhNTf_2$/KHMDS. However, unfortunately, the reaction gave a complex mixture containing a trace amount of the desired cyclic ketene acetal triflate **14**.[12,13] To improve this process, we next examined the effect of the protective group of the substrates.

Table 1 summarizes the results of the reactions using various substrates.[14] Compared with the case of **13** (entry 1), the reaction was slightly improved when 4-methoxybenzylidene acetal was used as a protective group giving the product **16** in 10% yield. A reasonable yield was obtained by the reaction of **17** having an acetonide protection (entry 3). The desired cyclic ketene acetal triflate **18** was obtained in 79% yield. On the other hand, no reaction took place with bis-TBS ether derivative **19** (entry 4). Although the reason is not clear yet, the changing the protective group would affect on the conformation of the 8-membered lactone ring to stabilize the resulting potassium enolate.

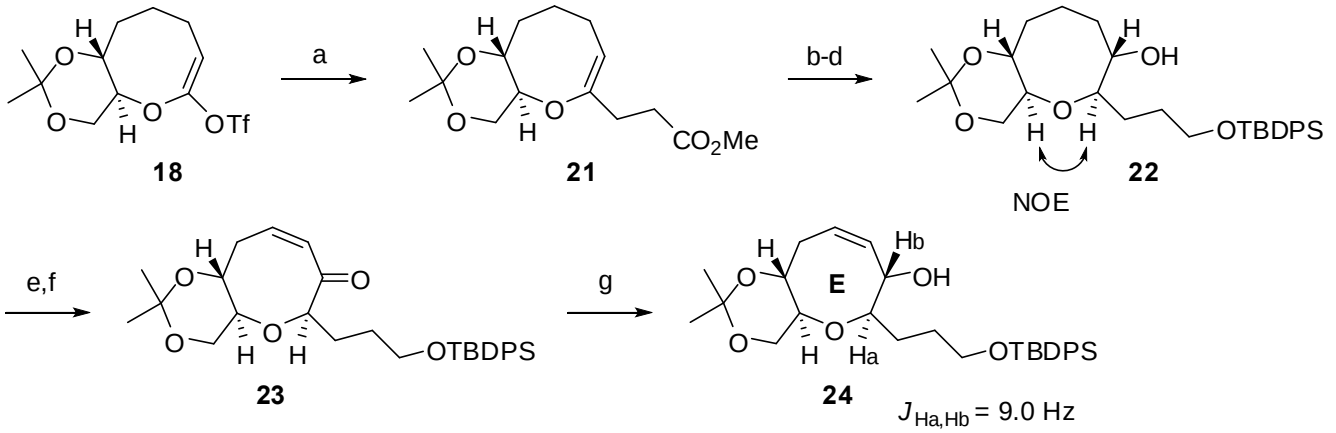
Table 1. The reaction of lactones with $PhNTf_2$/KHMDS[a]



entry	lactone	triflate	yield[b]
1	 **13**	 **14**	trace
2	 **15**	 **16**	10%
3	 **17**	 **18**	79%
4	 **19**	 **20**	0%

[a]The reactions were carried out with 2 equiv of $PhNTf_2$, 2.5 equiv of KHMDS, and 3 equiv of DMPU in THF at -78 °C. [b]Isolated yields

The cyclic ketene acetal triflate **18** obtained was then subjected to the key C-C bond formation. Thus, the Negishi coupling of **18** was carried out with zinc homoenolate **4** in the presence of $PdCl_2(o\text{-}Tol_3P)_2$[8] to give cyclic enol ether **21** in 70% yield. Reduction of the ester **21** with $LiAlH_4$, followed by protection of the resulting alcohol with TBDPSCl/imidazole provided the corresponding silyl ether, which was subjected to the hydroboration with thexylborane and oxidation to afford hydroxyl cyclic ether **22** as a single stereoisomer in 34% overall yield. The *cis*-relationship of the two alkyl groups on the ether ring was confirmed by ^{1}H NMR analysis and NOE experiments. The Dess-Martin reaction of the alcohol **22** and subsequent Ito-Saegusa oxidation[15] of the resulting ketone gave enone **23** in 72% overall yield. Stereoselective reduction of the enone **23** was performed by using $NaBH_4/CeCl_3$ to furnished a 5:1 mixture of the desired E ring segment **24** and its diastereomer in 97% combined yield. The coupling constants, $J_{Ha,Hb}$ = 9.0 Hz, clearly indicated the *trans*-relationship of H_a and H_b protons.



Scheme 3. Reagents and conditions: (a) **4**, $PdCl_2(o\text{-}Tol_3P)_2$, benzene, 40 ºC, 70%; (b) $LiAlH_4$, ether, 0 ºC; (c) TBDPSCl, imidazole, CH_2Cl_2, rt; (d) Thexylborane, THF, 0 ºC, then 1N NaOH, 30% H_2O_2, 34% (3 steps); (e) Dess-Martin periodinane, CH_2Cl_2, rt; (f) KHMDS, TMSCl, Et_3N, THF, -78 ºC; (ii) $Pd(OAc)_2$, MeCN, rt, 72% (3 steps); (g) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, -78 ºC,. 97% (5:1).

In conclusion, the stereocontrolled synthesis of the E ring segment of ciguatoxin CTX3C was achieved by using the Negishi coupling of an 8-membered cyclic ketene acetal triflates. Although the details are not clear yet, the effect of the protective groups on the triflation reaction is of interest. Further studies towards the total synthesis of **1** are in progress in our laboratories.

ACKNOWLEDGEMENTS

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