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Acetylene cobalt complex and vinylsilane strategy in the synthesis of ciguatoxin (D)EF analog

Kazunobu Kira and Minoru Isobe*

Laboratory of Organic Chemistry, Graduate School of Bioagricultural Sciences, Nagoya University, Chikusa, Nagoya 464-8601, Japan

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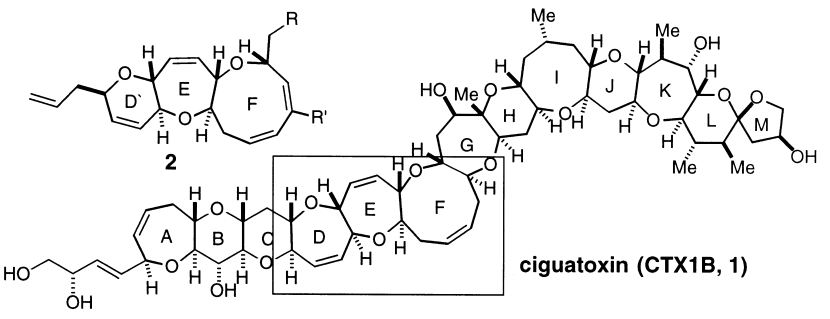
Abstract

A synthetic route to the (D)EF analog of ciguatoxin has been explored through acetylene cobalt complex and vinylsilane strategy. The central reactions in the synthesis are: (i) ether ring formation mediated by acetylene cobalt complex and (ii) decomplexation of the *endo*-acetylene cobalt complexes to vinylsilanes or olefins. Unusual rearrangement of epoxy-silane to allylic alcohol is also described.

Keywords: ciguatoxin; acetylene cobalt complex; hydrosilylation; vinylsilane.

We have been studying various synthetic methodologies applicable to the ciguatoxin (CTX1B, **1**)[1] class of natural products, that have *syn*/*trans* stereochemistry of polycyclic oxy-ring systems. Our synthetic efforts have recently culminated in both enantiomeric forms of the left end segment (ABC)[2] or right middle segment, including the HIJK segment.[3] These studies base their strategy on the chemistry of sugar acetylene[4] and acetylene biscobalthexacarbonyl complex.[5] Interesting synthetic efforts have been reported from other research groups lead by Hirama,[6] Tachibana[7] and Murai[8] based upon various different methodologies.[9]



* Corresponding author. Tel: +81-52-789-4109; fax: +81-52-789-4111; e-mail: isobem@agr.nagoya-u.ac.jp

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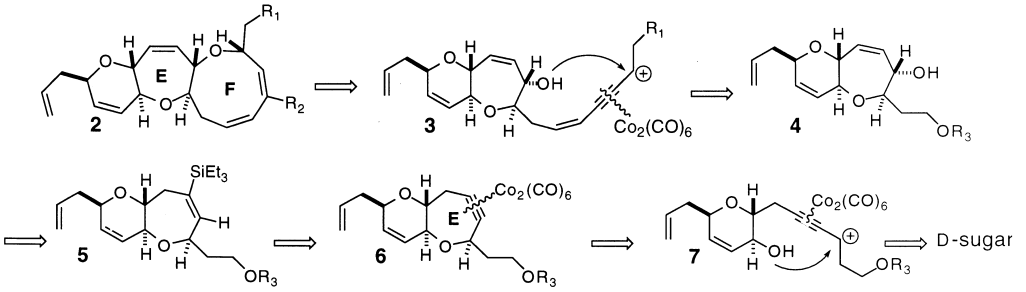
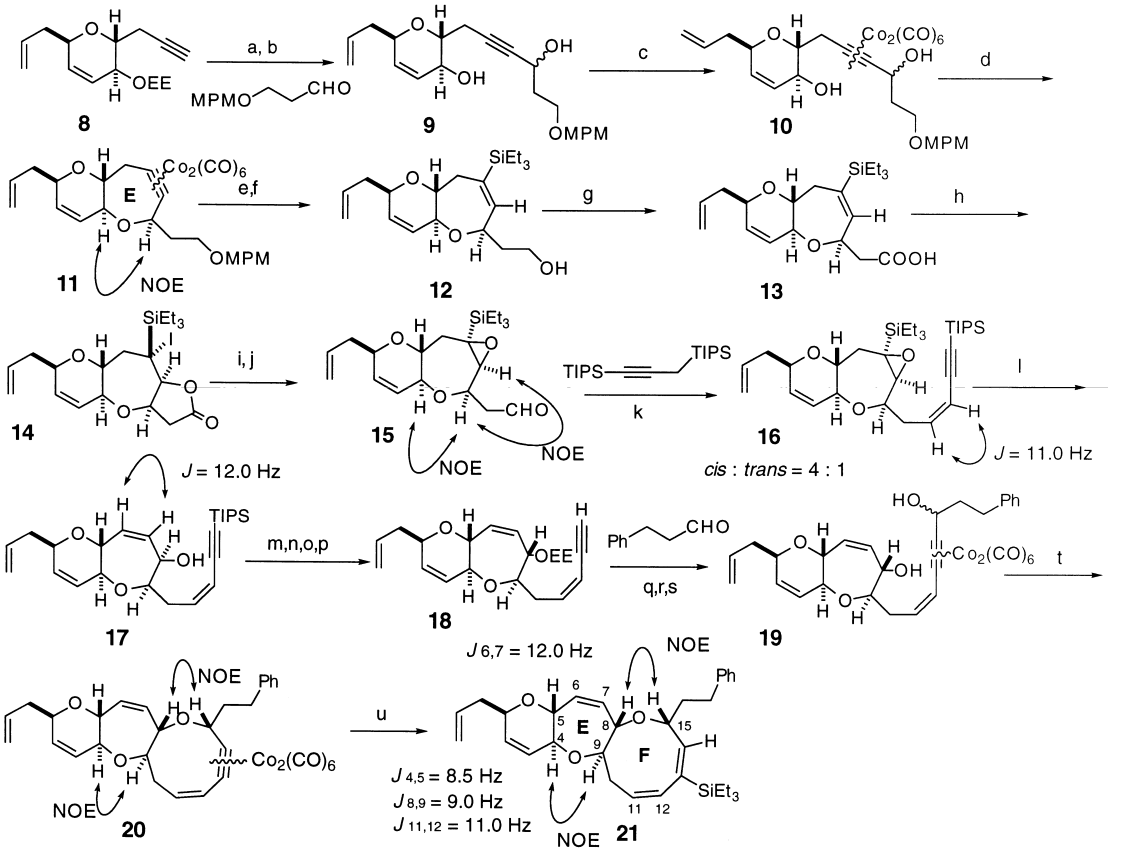
This communication includes the synthesis of the left middle segment (D)EF in the form of **2** to explore our methodologies, which commences from a D-hexopyranose derivative (D′ ring) to extend the carbon chain toward the E/F ring and subsequent cyclization to the medium-sized ether rings. Retrosynthetic analysis is illustrated in Scheme 1, where the critical nine-membered ring cyclization would occur from the precursor propargylic cation **3** that is stabilized by an acetylene cobalt complex.[10] This eneyne could be derived from the allylic alcohol **4**. This allylic alcohol should be transformed from the complex **6** via vinylsilane **5**. Similar cyclization of the seven-membered ring from the precursor propargylic cation **7** again took the form of the acetylene cobalt complex. A D-pyranose derivative would have access to this starting material, as reported previously.[11]



Scheme 1. Retrosynthesis of (D)EF analog **2**

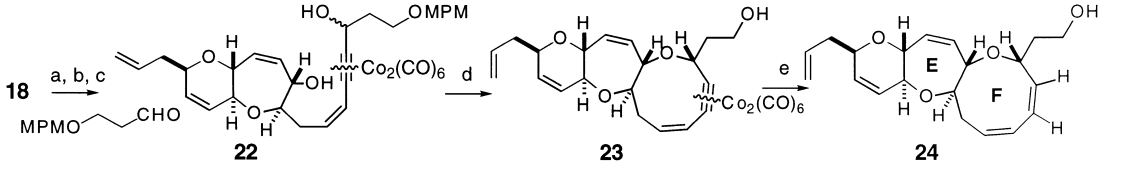
An optically active compound **8** (preparable from triacetyl-D-glucal in 9 steps[11]) was selected as a template to extend the carbon chain as analyzed in retrosynthesis (Scheme 1). The lithium acetylide of **8** was added to the protected 3-oxy-propanal to give **9**, which was converted into cobalt complex **10**. The crucial cyclization happened by treatment with *p*-toluenesulfonic acid to give **11** in *syn*/*trans* manner as a single isomer.[12] Hydrosilylation[13] of **11** with triethylsilane in hot toluene was followed by oxidative deprotection of the *p*-methoxybenzyl group with DDQ to afford **12**. The epoxidation of the silyl olefin in **12** was not stereoselective with *m*CPBA, but it gave a mixture of α- and β-epoxides (5:3) without touching the other olefins. Only one of these epoxides, the β-epoxide, turned out to be convertible to the allylic alcohol by treatment with $BF_3{\cdot}OEt_2$ in a separate experiment.[14] Finally, β-epoxide was stereoselectively prepared from **12**, firstly by oxidation to the carboxylic acid **13**, secondly by iodo-lactonization to **14** and its DIBAL reduction to afford the β-epoxide **15**. Peterson olefination of this aldehyde **15** with 3-lithio-1,3-bis-(triisopropylsilyl)-propyne[15] gave largely the *cis* ene-yne **16**. Treatment of this epoxysilane **16** with $BF_3{\cdot}OEt_2$ yielded the allylic alcohol **17** in 80%. Now the configuration of C-8 with the hydroxyl group was inverted by Mitsunobu reaction to convert into **18**. Addition of the lithium acetylide of **18** to phenylpropanal provided a propargylic alcohol, which was further converted into cobalt complex **19**. Its cyclization was performed by simple treatment with $BF_3{\cdot}OEt_2$ at room temperature to afford **20** in 70% yield as a single stereoisomer. *Syn* stereochemistry of this product was shown by NOE experiments.[16] This cobalt complex was hydrosilylated into the vinylsilane **21** by simple heating with triethylsilane[13] (Scheme 2).

As shown in Scheme 3, an alternative synthesis of a similar compound was achieved. Addition of the lithium acetylide of **18** to a protected propanal successively converted it into the corresponding acetylene cobalt complex **22**, which was similarly cyclized with $BF_3{\cdot}OEt_2$ at a room temperature to give **23** in 81% yield as a single stereoisomer. Finally, the cobalt complex was decomplexed into the corresponding olefin **24** by simple heating with tributyltin hydride.[13]



Scheme 2. (a) *n*-BuLi/THF; (b) PPS/MeOH, 80% in two steps; (c) $Co_2(CO)_8/CH_2Cl_2$, 88%; (d) *p*TsOH·H_2O/CH_2Cl_2, rt, 90%; (e) Et_3SiH/toluene, 70°C; (f) DDQ, 80% in two steps; (g) Jones reagent; (h) $I(collidine)_2PF_6/CH_2Cl_2$, 77% in two steps; (i) DIBAL; (j) DBU, 85% in two steps; (k) *n*-BuLi/THF, –78°C to rt, 77%; (l) $BF_3{\cdot}OEt_2/CH_2Cl_2$, 80%; (m) TBAF/THF, quant.; (n) PPh_3, DEAD, benzoic acid, quant.; (o) K_2CO_3, MeOH; (p) EVE, PPTS, 76% in two steps; (q) *n*-BuLi; (r) PPTS, 87% in two steps; (s) $Co_2(CO)_8/CH_2Cl_2$, 78%; (t) $BF_3{\cdot}OEt_2/CH_2Cl_2$, rt, 70%; (u) Et_3SiH/toluene, 70°C, quant.

Although the junction protons of this particular compound have considerable overlap with each other and no NOE data are available to prove the *syn*/*trans* stereochemistry of **24** (Scheme 3).



Scheme 3. (a) *n*-BuLi; (b) PPTS/MeOH, 80% in two steps; (c) $Co_2(CO)_8/CH_2Cl_2$, 87%; (d) $BF_3{\cdot}OEt_2/CH_2Cl_2$, rt, 81%; (e) *n*-$Bu_3SnH$/toluene, 62%

Thus, we succeeded in the synthesis of the (D)EF analogs (**21** and **24**) of ciguatoxin **1** using acetylene cobalt complex and the unusual rearrangement of epoxysilane **15** to allylalcohol **16**. Further efforts directed toward the total synthesis of ciguatoxin are in progress in our laboratory.

Acknowledgements

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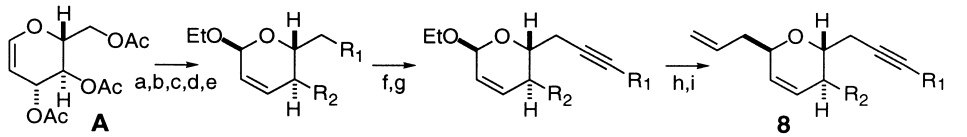
11. The starting material **8** was prepared in nine steps from triacetyl-D-glucal **A**.



a) EtOH $BF_3{\cdot}OEt_2/CH_2Cl_2$ 77%. b) Et_3N/MeOH-H_2O quant. c) TsCl, Py/CH_2Cl_2. d) NaI/acetone reflux. e) EVE, PPTS/CH_2Cl_2 87% in 2 steps. f) $Me_3SiC{\equiv}CLi$/THF-HMPA r.t. g) K_2CO_3/MeOH 70% in 2 steps. h) $Me_3SiCH_2CH{=}CH_2$ $BF_3{\cdot}OEt_2/CH_2Cl_2$. i) EVE, PPTS/CH_2Cl_2 92% in 2 steps.

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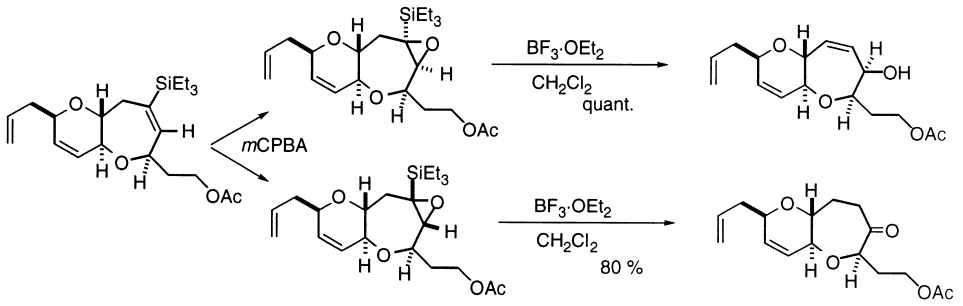
14. Acid treatment of α- and β-epoxysilane gives ketone and allylic alcohol, respectively.



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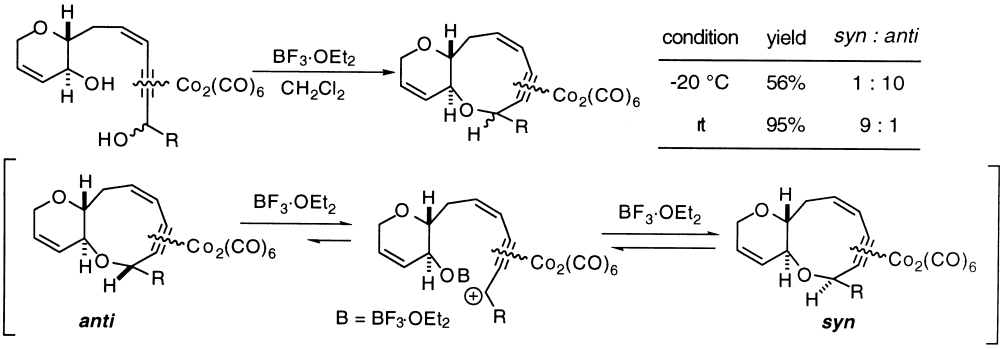
16. Stereochemistry of cyclic products is governed by reaction conditions; the *anti* isomer is the kinetic product, while the *syn* isomer is the thermodynamic product.



condition	yield	*syn : anti*
-20 °C	56%	1 : 10
rt	95%	9 : 1