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

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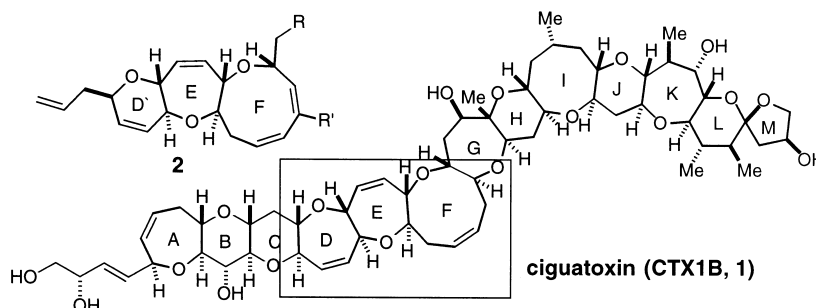
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Abstract

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. © 2000 Elsevier Science Ltd. All rights reserved.

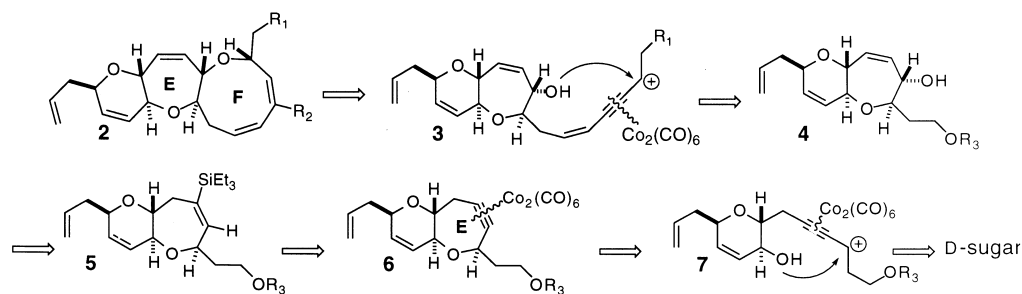
Keywords: ciguatoxin; acetylene cobalt complex; hydrosilylation; vinylsilane.

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 acetylene⁴ and acetylene biscobalthexacarbonyl complex.⁵ Interesting synthetic efforts have been reported from other research groups lead by Hirama,⁶ Tachibana⁷ and Murai⁸ based upon various different methodologies.⁹



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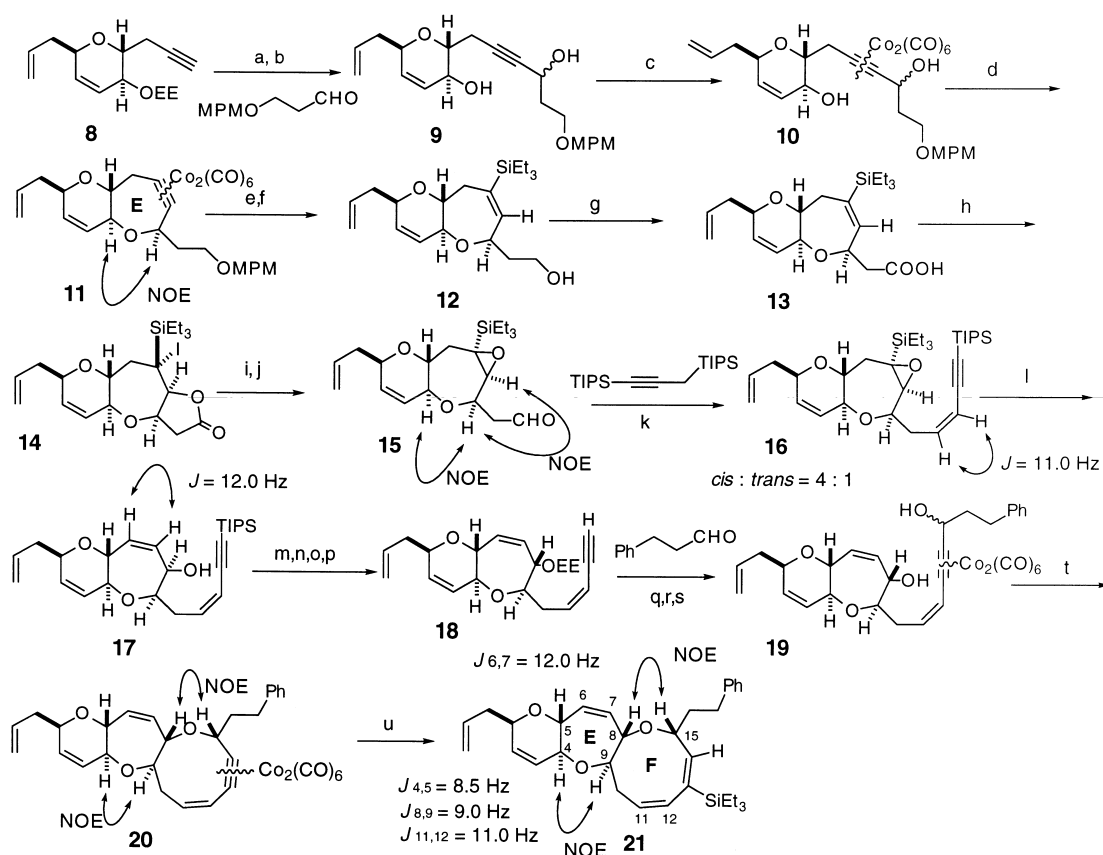
This communication includes the synthesis of the left middle segment (D)EF in the form of **2** to explore our methodologies, which commences from a D-hexopyranose derivative (D' ring) to extend the carbon chain toward the E/F ring and subsequent cyclization to the medium-sized ether rings. Retrosynthetic 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



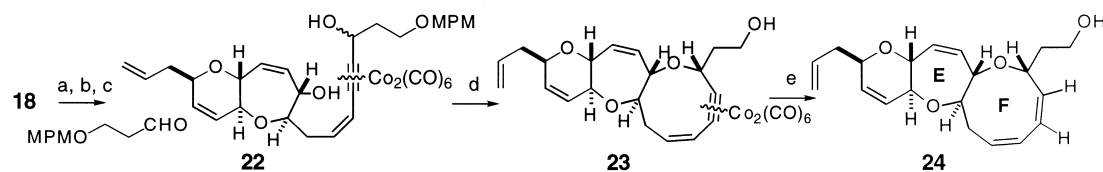
Scheme 1. Retrosynthesis of (D)EF analog **2**

An optically active compound **8** (preparable from triacetyl-D-glucal in 9 steps¹¹) 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 Hydrosilylation¹³ 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 $\text{BF}_3 \cdot \text{OEt}_2$ 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)-propyne¹⁵ gave largely the *cis* ene-yne **16**. Treatment of this epoxysilane **16** with $\text{BF}_3 \cdot \text{OEt}_2$ 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 $\text{BF}_3 \cdot \text{OEt}_2$ 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 triethylsilane¹³ (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 $\text{BF}_3 \cdot \text{OEt}_2$ 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



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).



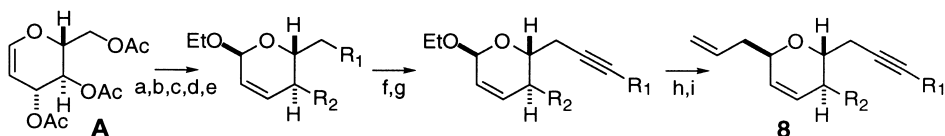
Thus, we succeeded in the synthesis of the (D)EF analogs (**21** and **24**) of ciguatoxin **1** using acetylene cobalt complex and the unusual rearrangement of epoxysilane **15** to allyl alcohol **16**. Further efforts directed toward the total synthesis of ciguatoxin are in progress in our laboratory.

Acknowledgements

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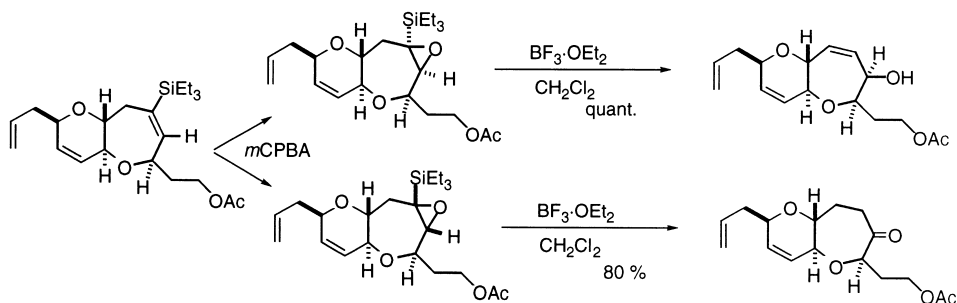
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11. The starting material **8** was prepared in nine steps from triacetyl-D-glucal **A**.



- a) EtOH $\text{BF}_3 \cdot \text{OEt}_2 / \text{CH}_2\text{Cl}_2$ 77%. b) $\text{Et}_3\text{N} / \text{MeOH} - \text{H}_2\text{O}$ quant. c) TsCl, Py/ CH_2Cl_2 . d) NaI/acetone reflux. e) EVE, PPTS/ CH_2Cl_2 87% in 2 steps. f) $\text{Me}_3\text{SiC}\equiv\text{CLi} / \text{THF} - \text{HMPA}$ r.t. g) $\text{K}_2\text{CO}_3 / \text{MeOH}$ 70% in 2 steps. h) $\text{Me}_3\text{SiCH}_2\text{CH}=\text{CH}_2$ $\text{BF}_3 \cdot \text{OEt}_2 / \text{CH}_2\text{Cl}_2$. 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.

