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Synthesis of the BCDE rings of ciguatoxin 1B via an acetylene biscobalthexacarbonyl–vinylsilane strategy

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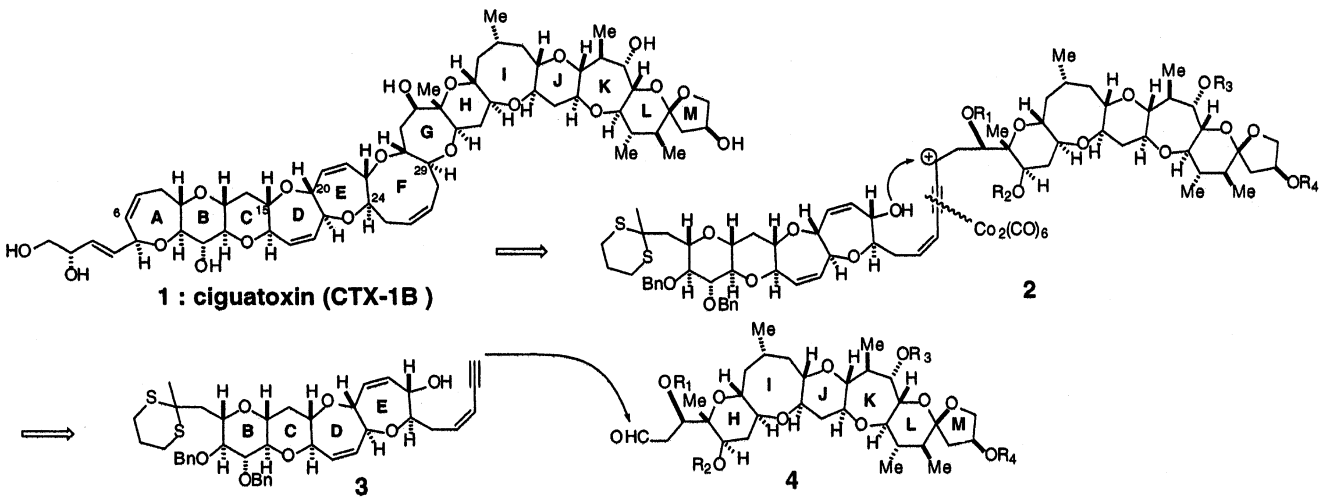
Abstract—A synthetic route to the BCDE rings of ciguatoxin 1B has been explored through acetylene biscobalthexacarbonyl complex and vinylsilane strategy. The key issues in the current synthesis are (i) ether ring cyclization by means of the acetylene cobalt complex and (ii) reductive decomplexation of the product *endo*-complexes into the corresponding vinylsilanes. A sequential cyclization route is also described along this line.

Ciguatoxin 1B (CTX 1B, **1**) is a major component in the creation of ciguatera poisoning. This structure was elucidated by Yasumoto et al.[1] Due to the limitation of the availability from nature, much effort has been paid to the synthetic studies.[2] We have recently explored various methodologies toward the total synthesis of **1**, which include *C*-alkynylation to sugar acetylenes,[3] acetylene biscobalthexacarbonyl complexes for medium size ether ring formation,[4] and reductive decomplexation to *cis*-olefins or vinylsilanes.[5] In this communication, we report the synthesis of a tetracyclic BCDE ring portion as the left part of **1** with special references to the employment of the above methodologies. The key issue is cationic cyclization with highly stereoselective *syn–trans* manner for the ladder shape target molecule. Our previous studies have culminated in the synthesis of ABC rings with the side chain,[6] D′EF rings[7] and H′IJK rings.[8] We planned the total synthesis of **1** as in Schemes 1 and 3, where the A-ring cyclization will be achieved at the latest stage from **2**. The coupling step between an anion of **3** and an aldehyde **4** would be followed by the cyclization of F- and G-rings. In this report we focus on the synthesis of the left half of **1** in the form of compound **3**.



Scheme 1.

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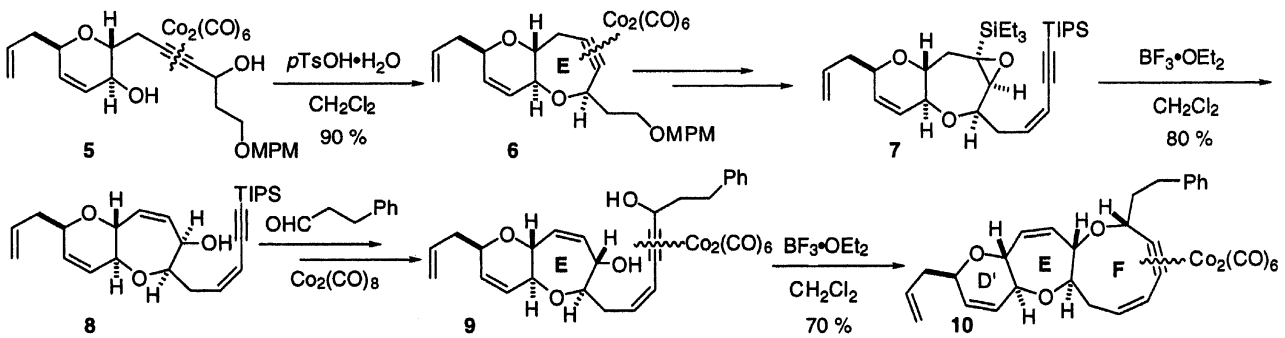
We have recently reported the synthesis of a D′EF analog[7] **10** of CTX 1B as shown in Scheme 2. The key issues are the sequential route of the *endo* cobalt complex **6** to another complex **10** via steps including cyclization, hydrosilylation (to vinyl silane), transformation of the epoxysilane **7** to allylic alcohol **8** and then cyclization of the precursor **9** to the new complex **10**. We employed this methodology in the synthesis of **3** as summarized in the retrosynthetic analysis in Scheme 3. The E-ring allylic alcohol in **3** would be cyclized from the precursor cation[9] **11** and the D-ring having a similar allylic alcohol in **13** would be derived from the cation **14**. The starting material was selected to be **15**.[10]

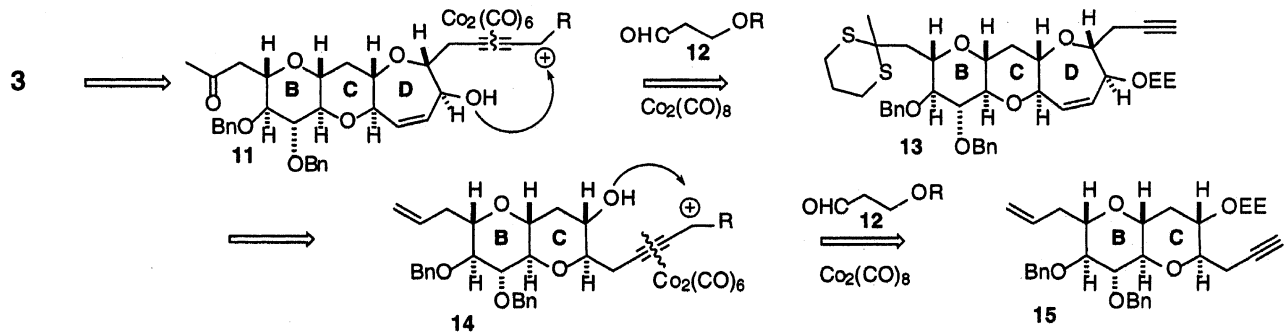
The synthetic route leading to **3** of CTX-1B (**1**) is illustrated in Scheme 4 commencing from **16**. Preparation of this material having a different protective group was previously reported[6c] and it was converted into the dibromoolefin **18** as an equivalent precursor of acetylene **15**.[10] Treatment of the dibromoolefin **18** with *n*-BuLi generated the corresponding acetylide, which was mixed with the aldehyde **19** to give the propargyl alcohol **20**. After deprotection of the hydroxyl groups, it was successively treated with $Co_2(CO)_8$ and then $BF_3{\cdot}OEt_2$ in one-pot to afford the cyclization product **21** as a single stereoisomer having a *syn–trans* relationship.[11] Hydrosilylation[5] of **21** was conducted with 20 equiv. of Et_3SiH by heating at 60°C in dichloroethane solvent in the presence of propargyl alcohol.[12] The product, vinyl silane **22** was isolated in 90% yield as the only isolable product with high regioselectivity. The stereochemistry was established from the NMR data. The primary alcohol and the terminal olefin in **22** were oxidized to give the methyl ketone–carboxylic acid **23** in two steps. Conversion of the terminal olefin was due to its reactive nature during the following iodo-lactonization step to provide a tetrahydrofuran by-product; thus Wacker oxidation was employed to protect this olefin. Iodo-lactonization of **23** was followed by protection of the methyl ketone to afford the dithioketal **24**. DIBAL-H reduction of this lactone and subsequent DBU treatment in THF solvent yielded the epoxysilane **25**. After converting the aldehyde **25** into the acetylene[13] **27**, the crucial acidic transformation[14] was achieved to provide the allylic alcohol **28** by treatment with $BF_3{\cdot}OEt_2$, and its configuration was corrected by a modified Mitsunobu inversion[15] and protected to afford **29**. Its *syn–trans* stereochemistry was also confirmed from the coupling constant 9.0 Hz between C19 and C20.

The method for the D-ring formation was employed for the E-ring formation by repeating the following steps; carbon chain elongation through the acetylide of **29** and cobalt complexation (**30**), cyclization (**31**), hydrosilylation (**32**),[16] epoxysilane (**33**), Peterson type carbon chain elongation to the *cis* ene-yne **35**,[17] transformation into the allylic alcohol **36** and finally the correction of the stereochemistry to provide **3** of CTX-1B.[18]

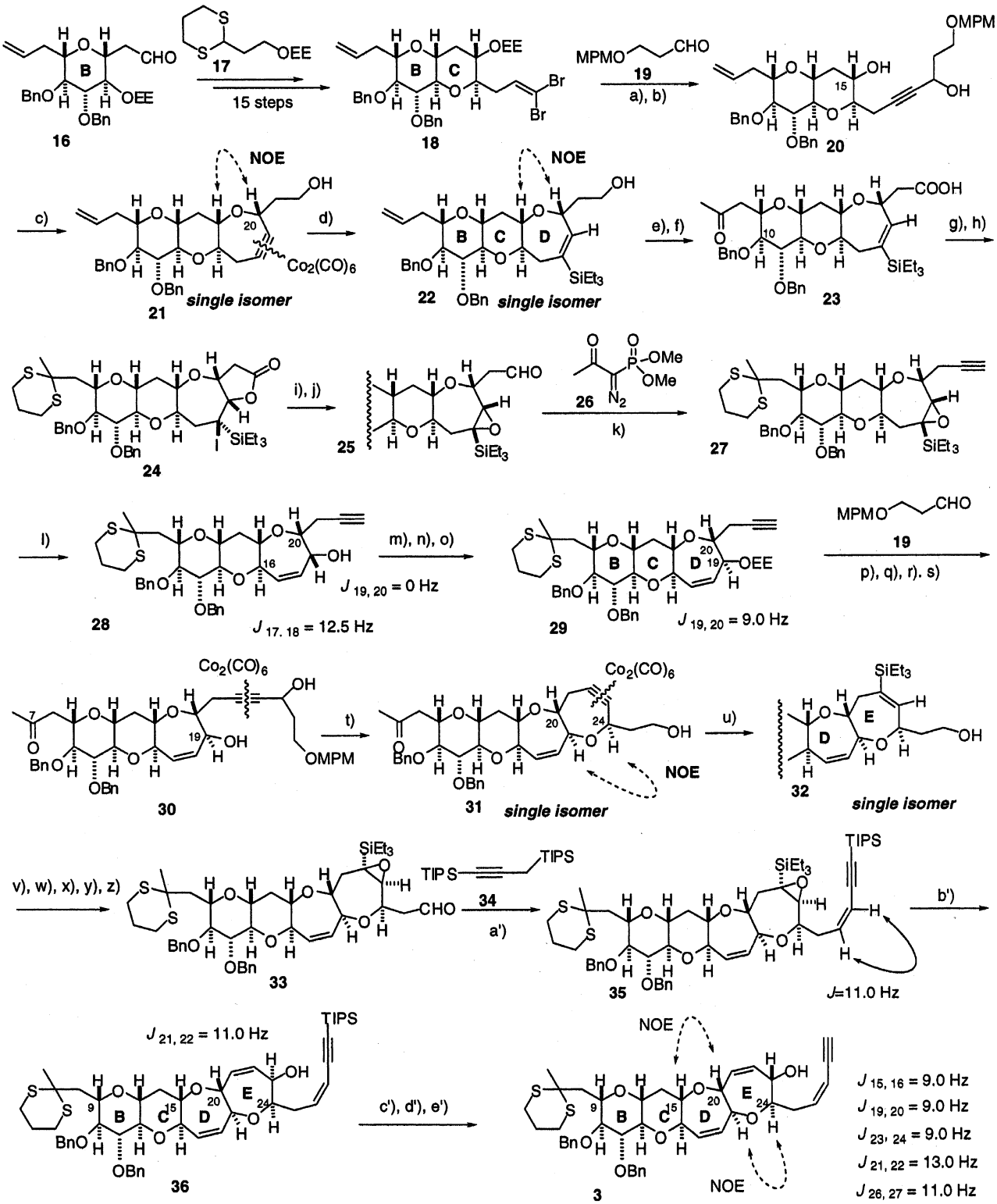
Further studies on **1** are now in progress and will be published elsewhere.



Scheme 2.



Scheme 3.



Scheme 4. Reagents, conditions and yields: (a) **18**, *n*-BuLi–THF then **19**; (b) Amberlyst-15E–MeOH, 80% in two steps; (c) $Co_2(CO)_8$–CH_2Cl_2 then $BF_3{\cdot}OEt_2$, 83%; (d) Et_3SiH, propargyl alcohol–$C_2H_4Cl_2$, 60°C, 90%; (e) Jones' reagent–acetone; (f) $PdCl_2$, CuCl–DMF–H_2O, 88% in two steps; (g) I(collidine)$_2PF_6$–CH_2Cl_2, 86%; (h) propanedithiol, $BF_3{\cdot}OEt_2$–CH_2Cl_2, 90%; (i) DIBAL-H–CH_2Cl_2; (j) DBU–THF, 88% in two steps; (k) dimethyl-1-diazo-2-oxopropylphosphonate **26**, K_2CO_3–MeOH, 81%; (l) $BF_3{\cdot}OEt_2$–CH_2Cl_2, 90%; (m) *p*-nitro benzoic acid, DEAD, PPh_3–toluene; (n) K_2CO_3–MeOH, 94% in two steps; (o) EVE, PPTS, CH_2Cl_2, quant.; (p) **29**, *n*-BuLi–THF then **19**; (q) Amberlyst-15E–MeOH, 88% in two steps; (r) $(CF_3CO_2)_2PhI$–CH_3CN–H_2O; (s) $Co_2(CO)_8$–CH_2Cl_2, 83% in two steps; (t) $BF_3{\cdot}OEt_2$–CH_2Cl_2, 86%; (u) Et_3SiH–$C_2H_4Cl_2$–EtOH, 60°C, quant.; (v) Jones' reagent–acetone; (w) I(collidine)$_2PF_6$–CH_2Cl_2; (x) propanedithiol, $BF_3{\cdot}OEt_2$–CH_2Cl_2, 63% in three steps; (y) DIBAL-H–CH_2Cl_2; (z) DBU–THF, 83% in two steps; (a′) *n*-BuLi, **34**, then **33**, 69%; (b′) $BF_3{\cdot}OEt_2$–CH_2Cl_2, 65%; (c′) TBAF, THF, 83%; (d′) *p*-nitro benzoic acid, DEAD, PPh_3–toluene; (e′) K_2CO_3–MeOH quant. in two steps.

Acknowledgements

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10. Compound **18** was prepared in 15 steps from B-ring aldehyde **16**. The analog of B-ring aldehyde **16** was already reported in Ref. 6c.
11. The stereochemistry of the cyclic products is governed by the reaction condition, the *anti* isomer being the kinetic product and the *syn* isomer being the thermodynamic product.
12. Propargyl alcohol was added to prevent isomerization of the terminal olefin to the inner olefin and silylation of the hydroxyl group at C22. The details will be reported separately.
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14. This transformation was reported under different condition, see: (a) Hudrik, P. F.; Wan, C.-N.; Withers, G. P. *Tetrahedron Lett.* **1976**, 1449–1452.; (b) Hudrlik, P. F.; Tafesse, L.; Hudrlik, A. M. *J. Am. Chem. Soc.* **1997**, *119*, 11689–11690.
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16. EtOH was added to prevent the silylation of the hydroxyl group at C26.
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18. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.51 (3H, s, H-6), 1.55 (1H, q, J=11.0 Hz, H-14a), 1.73–1.90 (2H, m, -$SCH_2CH_2CH_2$S-), 1.80 (1H, dd, J=15.0, 8.5 Hz, H-8a), 2.34 (1H, dt, J=11.0, 4.0 Hz, H-14b), 2.48 (1H, ddd, J=14.0, 5.5, 2.5 Hz, -$SCH_2CH_2CH_2$S-), 2.56 (1H, d, J=15.0 Hz, H-8b), 2.56–2.63 (1H, m, -$SCH_2CH_2CH_2$S-), 2.66 (1H, dddd, J=14.5, 8.0, 6.5, 1.5 Hz, H-25a), 2.68 (1H, ddd, J=14.5, 11.0, 3.0 Hz, -$SCH_2CH_2CH_2$S-), 2.78 (1H, dddd, J=14.5, 7.0, 3.5, 1.5 Hz, H-25b), 2.79 (1H, ddd, J=14.5, 11.0, 3.0 Hz, -$SCH_2CH_2CH_2$S-), 3.09-3.14 (2H, m, H-12, 13), 3.13 (1H, dd, J=2.5, 0.7 Hz, H-29), 3.24 (1H, dd, J=9.5, 8.5 Hz, H-10), 3.33 (1H, ddd, J=11.5, 9.0, 4.5 Hz, H-15), 3.50 (1H, ddd, J=9.0, 6.5, 3.5 Hz, H-24), 3.56 (1H, dd, J=9.5, 8.5 Hz, H-9), 3.64 (1H, t, J=8.5 Hz, H-11), 3.83 (1H, dq, J=9.0, 2.0 Hz, H-16), 4.01 (1H, dq, J=9.0, 2.0 Hz, H-20), 4.08 (1H, dq, J=9.0, 2.0 Hz, H-19), 4.11 (1H, m, H-23), 4.62 (1H, d, J=11.2 Hz, -OCH_2Ph), 4.77 (1H, d, J=11.2 Hz, -OCH_2Ph*), 4.98 (1H, d, J=11.2 Hz, -OCH_2Ph*), 5.01 (1H, d, J=11.2 Hz, -OCH_2Ph), 5.54 (1H, dt, J=13.0, 2.0 Hz, H-21), 5.61 (1H, ddm, J=11.0, 2.5 Hz, H-27), 5.63-5.70 (3H, m, H-17, 18, 22), 6.18 (1H, dddd, J=11.0, 8.0, 7.0, 0.7 Hz, H-26), 7.26–7.38 (10H, m, aromatic). TOF MS calcd for $C_{41}H_{49}O_7S_2$ 717.284 $[M+H]^+$. Found 717.285.