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CONVERGENT STRATEGY FOR SYNTHESIZING POLYCYCLIC ETHER MARINE TOXINS: SYNTHESIS OF THE ABCDE RING FRAGMENT OF CIGUATOXIN CTX3C‡

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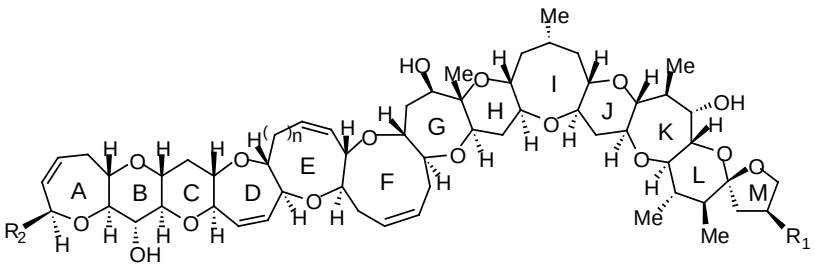
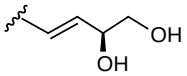
Abstract - The ABCDE ring fragment of CTX3C, the most important member of the ciguatoxin family, was concisely synthesized by extensive use of ring-closing olefin metathesis.

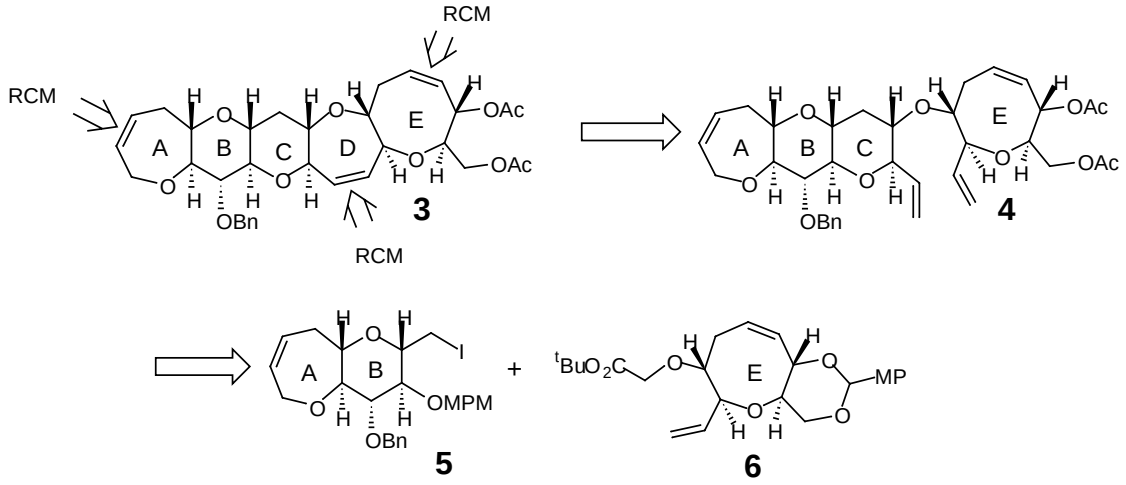
Ciguatoxin (CTX1B, **1**) and its congener, CTX3C (**2**), which possess gigantic structure and unique agonist activity against the sodium channel, are the principal toxin that causes 'ciguatera' seafood poisoning.[1] During the course of our synthetic studies into ciguatoxins,[2,3] we have recently succeeded in synthesizing the ABCDE ring framework[4] of **1** based on alkylation and ring-closing metathesis (RCM).[5] We describe herein a convergent synthesis of the ABCDE ring fragment (**3**) of **2**.



Ciguatoxin (CTX1B, **1**) n=0, R_1 = OH, R_2 = 

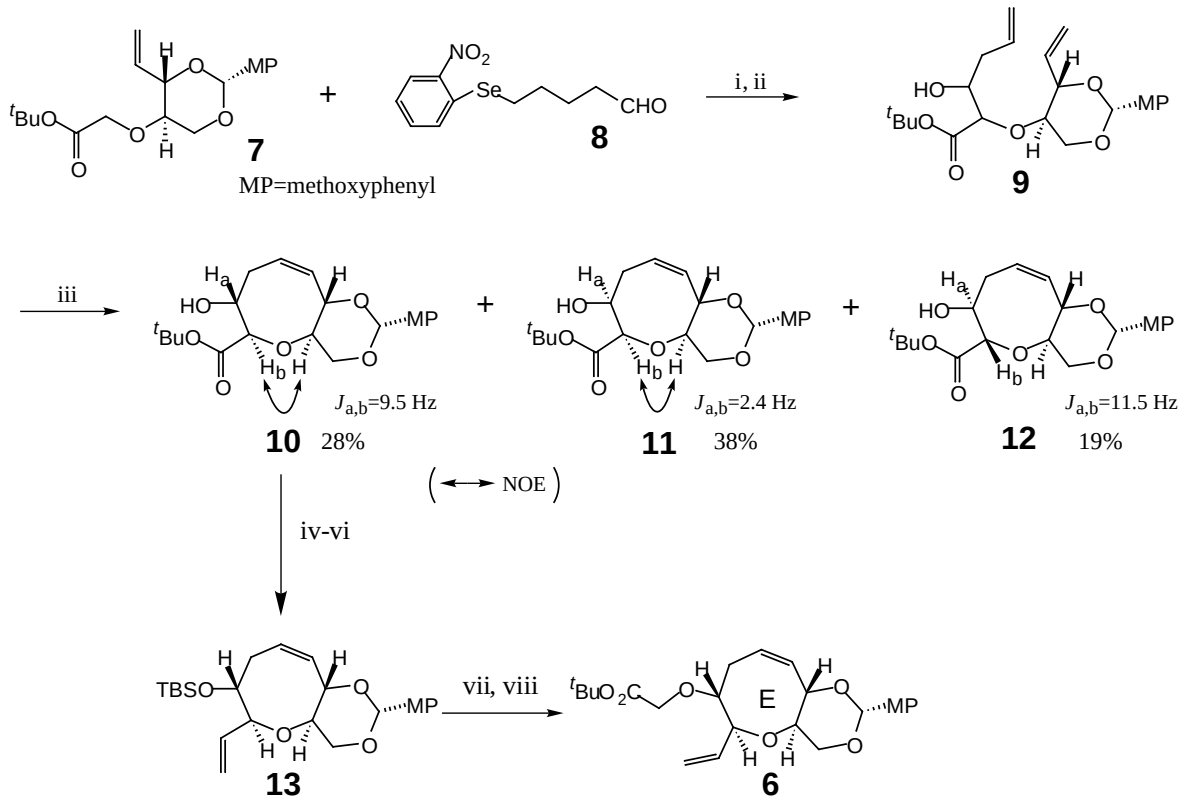
CTX3C, **2** n=1, R_1 = R_2 = H

‡ Dedicated to Professor Shô Itô on occasion of his 77th birthday



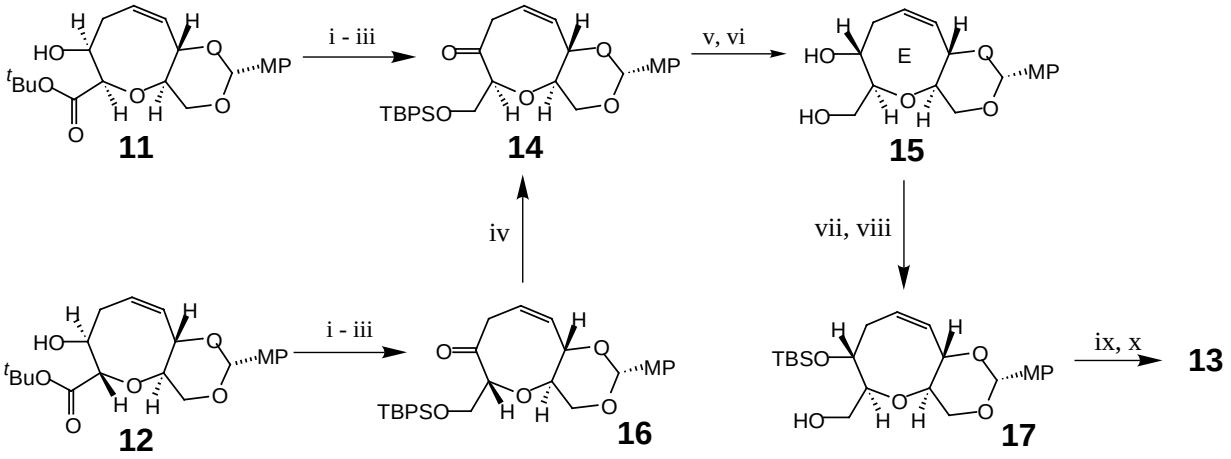
Scheme 1

Our hypothesis was to use RCM extensively for constructing seven- and eight-membered ring systems of **3** (Scheme 1). A precursor (**4**) of **3** would be prepared from the AB ring (**5**)[4] and the E ring fragment (**6**) utilizing the alkylation-metathesis sequence. The last RCM step (**4** → **3**) may be a crucial step because the double bond in the E ring might react competitively.



Scheme 2 *Reagents and conditions*: i) LDA, THF, -78 °C, 71%. ii) 30% H_2O_2, $NaHCO_3$, THF, 90%. iii) $(PCy_3)_2Cl_2Ru$=CHPh (7 mol %), CH_2Cl_2, reflux, 2 d, 85% (total). iv) TBSCl, imidazole, DMF, 93%. v) DIBALH, -78~-50 °C. vi) Ph_3PMeBr, KO^{t}Bu, THF, 53% (2 steps). vii) TBAF, THF, 99%. viii) *t*-butyl bromoacetate, NaH, 75%. TBSCl=*t*-butyldimethylsilyl chloride; DMF=*N*,*N*-dimethylformamide; DIBALH=diisobutylaluminum hydride; TBAF=tetrabutylammonium fluoride.

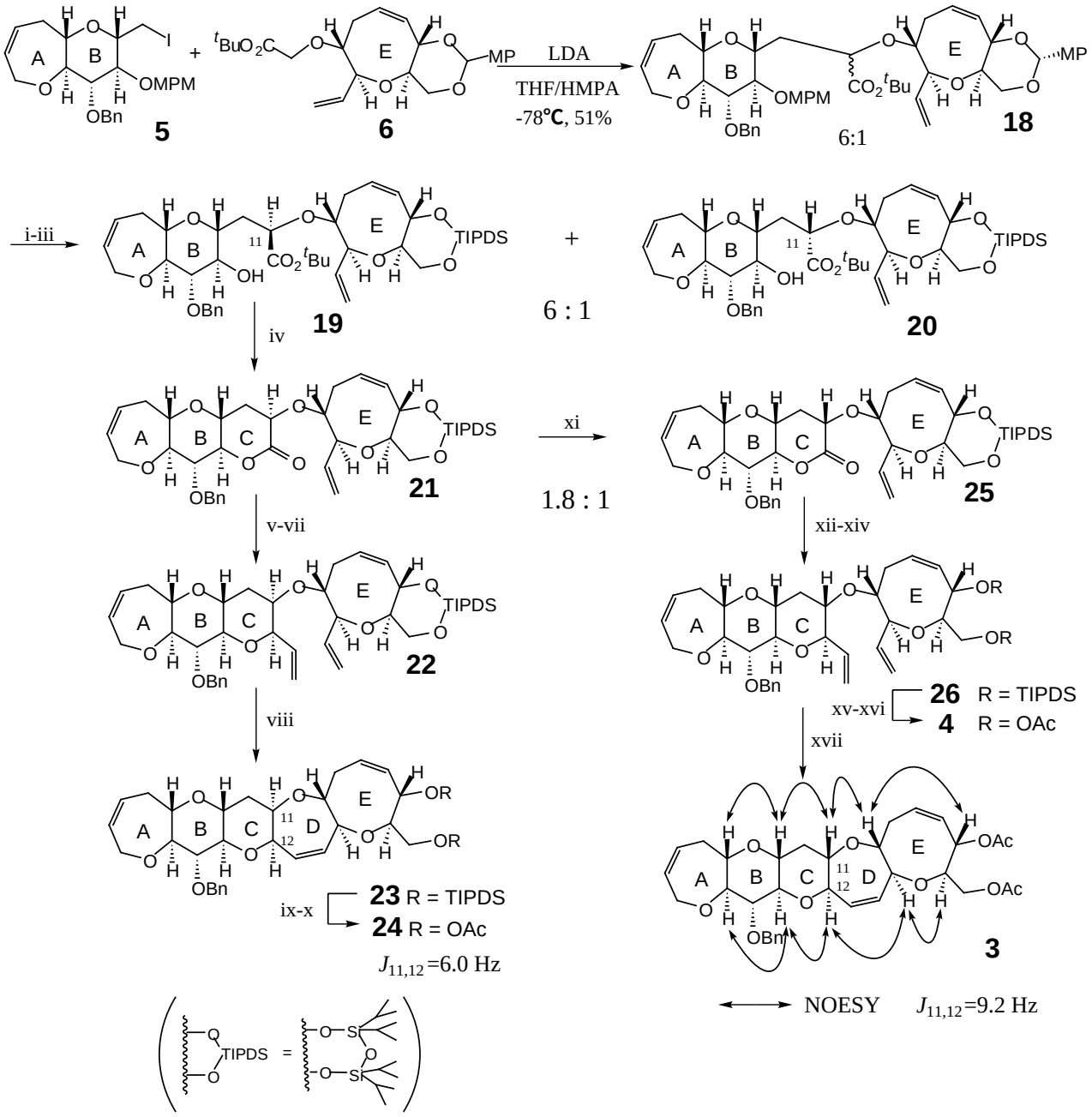
Synthesis of the E ring is shown in Scheme 2. Aldol reaction of ester (**7**)[6] with aldehyde (**8**)[6] followed by treatment with H_2O_2[7] gave diene (**9**) as an inseparable mixture of diastereomers. RCM reaction of **9** using Grubbs' catalyst[8] proceeded smoothly to afford eight-membered cyclic ethers (**10**, **11**, and **12**) in 28, 38 and 19% yields, respectively. Protection of the secondary alcohol of **10**, which has the required stereochemistry, and successive DIBALH reduction and Wittig reaction gave **13**. Deprotection of **13** followed by alkylation with *t*-butyl bromoacetate gave the glycolic acid ester derivative (**6**).



Scheme 3 *Reagents and conditions*: i) $LiAlH_4$, Et_2O, 95% (for **11**); 99% (for **12**). ii) TBPSCl, Et_3N, DMAP, CH_2Cl_2, 87%; 80%. iii) Dess-Martin periodinane, CH_2Cl_2, 88%; quant. iv) imidazole (5 mol eq.), toluene, 110 °C, 1 d, quant. v) TBAF, AcOH, THF, 75%. vi) $NaH(OAc)_3$, AcOH, MeCN, 93%. vii) TBSCl, imidazole, DMF, 98%. viii) neutral alumina, H_2O, hexane, 81%. ix) Dess-Martin periodinane, CH_2Cl_2. x) Ph_3PMeBr, KO^tBu, THF, 85% (2 steps). TBPSCl=*t*-butyldiphenylsilyl chloride; DMAP=4-(dimethylamino)pyridine; TBAF=tetrabutylammonium fluoride; TBSCl=*t*-butyldimethylsilyl chloride; DMF=*N*,*N*-dimethylformamide.

Although the yield of **10** is not high, other diastereomers (**11**) and (**12**) are all useful for the synthesis (Scheme 3). Reduction of the ester (**11**), followed by selective protection of the primary alcohol as TBPS ether, and oxidation of the secondary alcohol with Dess-Martin perioidinane gave a non-conjugated enone (**14**). Removal of the TBPS group of **14** and stereoselective reduction using $NaBH(OAc)_3$[9] gave diol (**15**) as a single isomer. The diol (**15**) was converted to **13** *via* selective deprotection of the corresponding bis-TBS ether using Guerrero's method,[10] and was followed by oxidation of **17** and subsequent Wittig reaction. The ester (**12**) was also converted to **13** *via* an enone (**16**) which was prepared in an analogous manner. Complete epimerization of **16** with imidazole[4, 11] gave the enone (**14**) without a migration of the double bond.

Alkylation of the E ring fragment (**6**) with the AB ring fragment (**5**)[4] gave a 51% yield of **18** as an inseparable 6:1 diastereomeric mixture (Scheme 4). Acidic methanolysis of the *p*-methoxybenzylidene acetal (**18**) followed by protection of the resulting 1,3-diol as TIPDS ether, and removal of the MPM group yielded an epimeric mixture of **19** and **20**, which were easily separated by silica gel column chromatography. Since the stereochemistry at C11 was ambiguous at this stage, we carried out further



Scheme 4 *Reagents and conditions*: i) PPTS, MeOH, 81%. ii) 1,3-dichlorotetraisopropyldisiloxane, 99%. iii) DDQ, CH_2Cl_2, 99%. iv) CSA, toluene, 70 °C, 70%. v) vinylmagnesium bromide, Et_2O, -78 °C, 59%. vi) $CH(OMe)_3$, CSA, CH_2Cl_2, 77%. vii) Et_3SiH, BF_3•Et_2O, -50~-30 °C, 85%. viii) $(PCy_3)_2Cl_2Ru$=CHPh (0.5 mol eq.), CH_2Cl_2, reflux, 1 d, 43%. ix) TBAF, THF. x) Ac_2O, py, 82% (2 steps). xi) imidazole, toluene, 110 °C, 85%. xii) vinylmagnesium bromide, Et_2O, -78 °C, 78%. xiii) $CH(OMe)_3$, CSA, CH_2Cl_2, 86%. xiv) Et_3SiH, BF_3•Et_2O, -50 °C, 87%. xv) TBAF, THF. xvi) Ac_2O, py, 82% (2 steps). xvii) $(PCy_3)_2Cl_2Ru$=CHPh (2.8 mol eq.), $CDCl_3$, 45 °C, 98%. HMPA=hexamethylphosphoric triamide; PPTS; pyridinium *p*-toluenesulfonate; DDQ=2,3-dichloro -5,6-dicyano-1,4-benzoquinone; CSA=10-camphorsulfonic acid; TBAF=tetrabutylammonium fluoride.

transformations using the major product (**19**). Acid treatment of **19** gave δ-lactone (**21**), which was converted to diene (**22**) in three steps: i) addition of vinylmagnesium bromide, ii) conversion of the resultant hemiacetal to the methyl acetal,[4] and iii) reduction of the acetal using Et_3SiH in the presence

of $BF_3 \cdot OEt_2$.[12] RCM reaction of **22** using Grubbs' catalyst afforded a pentacyclic system (**23**) without affecting the E ring. However, we found that the stereochemistry at C11 in **23** was not the required one by 1H NMR analysis of the corresponding diacetate (**24**). Attempts to improve the stereoselectivity in the alkylation reaction between the AB ring and E ring fragments using chiral auxiliary,[13] or epimerization of the ester (**18**)[14] were unsuccessful. However, the lactone (**21**) underwent epimerization upon treatment with imidazole[5,11] in toluene at 110 °C to give a separable 1.8:1 mixture of **21** and **25** at a 85% yield. The lactone (**25**) was converted to diene (**26**) in a manner analogous to **21**. The RCM reaction of **26** using Grubbs' catalyst gave an inseparable mixture of products including the desired pentacyclic ABCDE fragment. The diene (**26**) was then converted to a less hindered diacetate (**4**) in two steps at a 82% yield. The RCM reaction of **4** proceeded successfully without interference by the double bond in the E ring to give the ABCDE ring fragment of CTX3C (**3**) at a 98% yield. The stereochemistry of **3** was unambiguously determined by ^{1}H NMR analysis (NOESY experiment).[15]

In conclusion, we demonstrated that the alkylation-metathesis strategy is a highly effective method to synthesize the pentacyclic system (**3**) of **2**. Further studies directed toward the total synthesis of **2** are currently in progress in our laboratory.

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14 Epimerization of **18** did not proceed by any bases: imidazole, DBU, LDA, KO^{t}Bu, or $LiNEt_2$.

15 Phisical data for **3**; $[\alpha]^{29}{}_D$ –54.0° (c 0.28, $CHCl_3$). IR (film) ν 2932, 1749, 1508, 1243, 1092 cm^{-1}. MALDI-TOF MS (alpha) calcd for $C_{33}H_{40}O_{10}Na$ ($M+Na^+$) 619.2498, found 619.1809. HRMS (EI, 70 eV) calcd $C_{33}H_{40}O_{10}$ (M^+), 596.262, found 596.262. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.43 (1H, q, *J*=11.3 Hz, H10), 2.05 (3H, s), 2.06 (3H, s), 2.30 (1H, dt, *J*=11.3, 3.8 Hz, H10'), 2.30-2.35 (1H, m, H4), 2.33 (1H, dd, *J*=14.0, 9.0 Hz, H17), 2.64 (1H, ddd, *J*=16.1, 7.8,

3.5 Hz, H4'), 2.80 (1H, ddd, *J*=14.0, 10.0, 3.3 Hz, H17'), 3.06 (1H, t, *J*=9.0 Hz, H8), 3.11 (1H, td, *J*=9.0, 3.6 Hz, H9), 3.28 (1H, td, *J*=9.2, 3.8 Hz, H11), 3.28-3.33 (1H, m, H5), 3.33 (1H, t, *J*=8.3 Hz, H6), 3.47 (1H, t, *J*=8.3 Hz, H7), 3.67 (1H, dt, *J*=9.0, 3.0 Hz, H16), 3.71 (1H, ddd, *J*=10.0, 6.3, 2.1 Hz, H21), 3.80 (1H, ddd, *J*=9.2, 4.3, 2.5 Hz, H12), 4.01 (1H, ddd, *J*=15.4, 6.2, 3.0 Hz, H1), 4.11 (1H, dt, *J*=9.0, 2.2 Hz, H15), 4.16 (1H, dd, *J*=10.9, 2.2 Hz, H22), 4.22 (1H, dd, *J*=10.9, 6.3 Hz, H22'), 4.29 (1H, dd, *J*=15.4, 5.8 Hz, H1), 4.82 (2H, d, *J*=11.6 Hz, CH2Ph), 4.87 (2H, d, *J*=11.6 Hz, CH2Ph), 5.57 (1H, dd, *J*=11.0, 5.2 Hz, H20), 5.62 (1H, dt, *J*=12.5, 2.4 Hz, H14), 5.75-5.79 (2H, m, H3 and H19), 5.80 (1H, dt, *J*=12.5, 2.7 Hz, H13), 5.83-5.89 (2H, m, H2 and H18), 7.30-7.35 (3H, m), 7.38-7.41 (2H, m). ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.91, 21.03, 32.58, 34.64, 36.82, 64.67, 68.37, 70.48, 73.15, 74.81, 75.17, 75.49, 75.69, 75.96, 80.51, 81.76, 81.82, 82.08, 84.39, 87.39, 126.50, 126.73, 127.42, 127.52, 127.73, 128.19, 131.08, 131.34, 132.16, 134.42, 139.15, 168.61, 169.56.