Syntheses of the D-, E-, F-, and I-Ring Parts of Ciguatoxin by a Common Strategy Starting from Tri-*O*-acetyl-D-glucal

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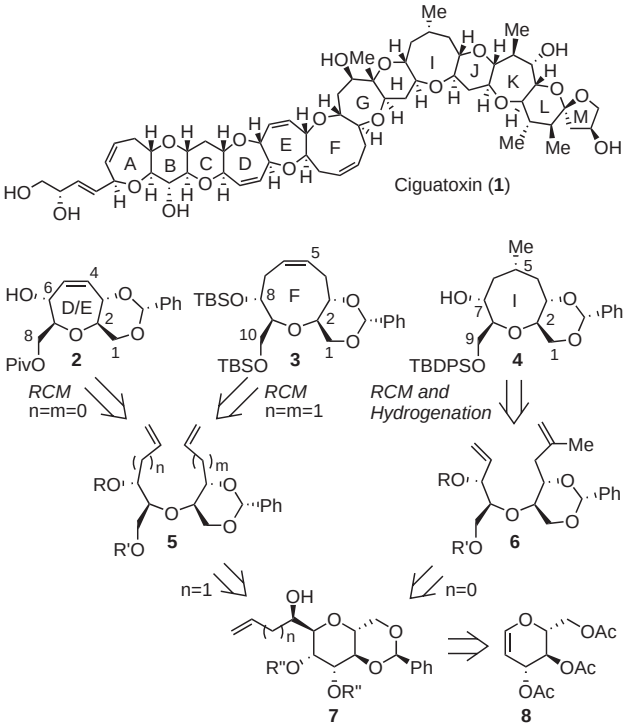
Abstract: Chiral medium-sized monocyclic ethers corresponding to the D-, E-, F-, and I-ring parts of ciguatoxin have been synthesized from tri-*O*-acetyl-D-glucal through a common synthetic route involving ring-closing olefin metathesis.

Key words: Heterocycles, stereoselective synthesis, natural products, ethers, metathesis

Ciguatoxin (**1**), isolated as one of the causative toxins of ciguatera sea food poisoning, has attracted much attention of synthetic chemists from its unique ladder-shaped polyether structure and strong bioactivity.[1–4] In the course of our studies toward the total synthesis of **1**,[5] we planned to construct the D-, E-, F-, and I-ring parts as the key synthetic intermediates. Here, the syntheses of oxepene **2** as the D- or E-ring part, oxonene **3** as the F-ring part, and oxocane **4** as the I-ring part by a common strategy starting from tri-*O*-acetyl-D-glucal (**8**) are described.

Our strategy for the syntheses of **2**, **3**, and **4** is outlined in Scheme 1. Oxepene **2** and oxonene **3** would be constructed readily from diene **5** by a ring-closing olefin metathesis (RCM) reaction.[6] On the other hand, oxocane **4** should be synthesized through a 2-step process [(i) a RCM reaction between vinyl and propen-2-yl groups of **6**[7] and (ii) the stereoselective reduction of the resultant trisubstituted olefin part]. The dienes **5** and **6** would be provided from *C*-glycoside **7**, having all requisite stereocenters, through a cleavage at the *cis*-diol part of the hexose ring.[8] Stereochemistry of **7** would be set up from tri-*O*-acetyl D-glucal (**8**) via diastereoselecive introduction of a 1-hydroxy-2-propenyl or 1-hydroxy-3-butenyl side chain.

Syntheses of intermediates **20** and **21** are shown in Scheme 2. Tri-*O*-acetyl-D-glucal (**8**) was converted to **10**[9] in 52% overall yield through a 3-step process [(i) treatment with TMSCN and $SnCl_4$,[10] (ii) removal of acetyl groups by methanolysis with Amberlyst 15, and (iii) benzylidene acetal formation]. In the latter two steps, no significant isomerization of a double bond at C3 to a conjugate system was observed. Olefin **10** was oxidized to diol **11** stereoselectively, which was protected with TBS



Scheme 1

to afford **12**. Nitrile **12** was reduced with DIBALH and the resulting imine was hydrolyzed under acidic conditions to produce aldehyde **13**. Stereoselective vinylation of **13** was succeeded with vinyl lithium prepared in situ from vinyl bromide and *t*-BuLi to give **14** in 79% isolated yield (dr 11:1).[11] On the other hand, **16** was obtained selectively by allylation of **13** with 2-allyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane[12] in 79% isolated yield (dr 3.8:1).[11] These alcohols **14** and **16** were converted to the corresponding cyclic phenyl boronates **20** and **21** in good yields by a 4-step sequence [(i) removal of TBS groups with TBAF; (ii) oxidative cleavage of 1,2-diol parts; (iii) reduction with $NaBH_4$; (iv) treatment with $PhB(OH)_2$].[13]

The D/E-ring part **2** was synthesized from **20** as shown in Scheme 3. Firstly, we examined a concise route. Alcohol **20** was converted to diene **24** in only three steps [(i) Swern oxidation, (ii) Wittig olefination, and (iii) removal of cyc-

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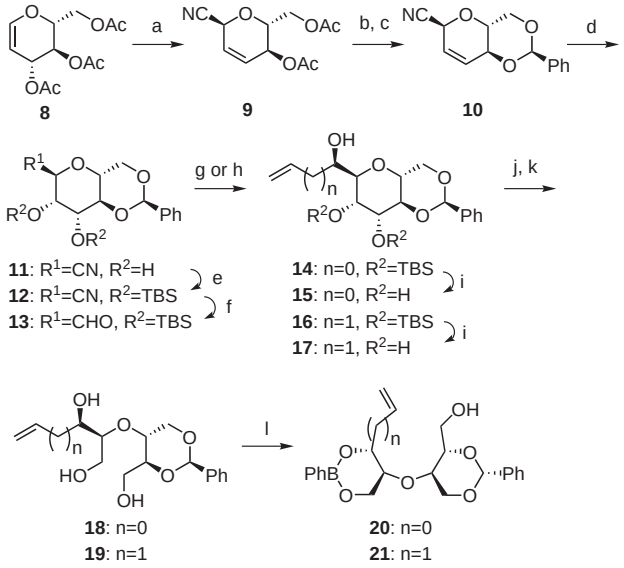
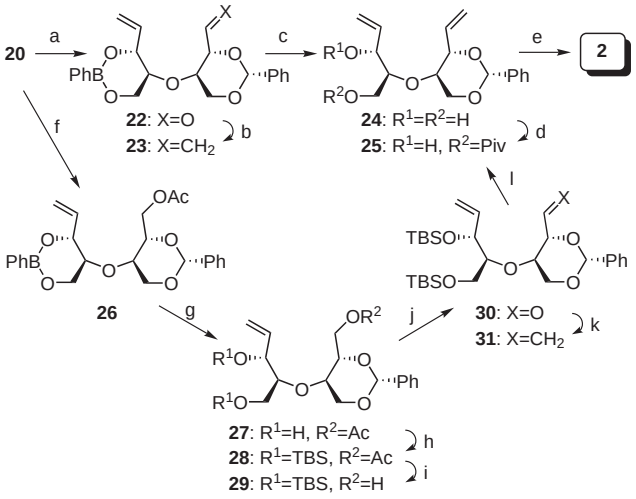


Scheme 2 Reagents and conditions. a) TMSCN (1.5 equiv), $SnCl_4$ (1.0 equiv), CH_2Cl_2, –78 °C, 10 min, then –20 °C, 10 min, 61%; b) Amberlyst 15, MeOH, reflux, 24 h; c) PhCHO (3 equiv), Amberlyst 15, $CHCl_3$, 23 °C, 19 h, then reflux with Dean–Stark trap, 3.5 h, 85% (2 steps); d) OsO_4 (0.01 equiv), NMO (1.4 equiv), 1,4-dioxane–H_2O (3:1), 20 °C, 4 d, ~100%; e) TBSOTf (3 equiv), 2,6-lutidine (6 equiv), CH_2Cl_2, 0 →22 °C, 72 h, ~100%; f) DIBALH (1 equiv), CH_2Cl_2, –78 °C, 12 min; 1 M HCl aq–CH_2Cl_2 22 °C, 16 h, 95%; g) CH_2=CHBr (6 equiv), *t*-BuLi (12 equiv), THF, –78 °C, 20 min, then **13**, –78 °C, 1 h, **14**: 79%; h) 2-allyl-4,4,5,5-tetramethyl-1,3-dioxo-2-borolane (6.5 equiv), CH_2Cl_2, –78 °C, 3.5 h, then –20 °C, 20 min, **16**: 79%; i) TBAF (3–3.5 equiv), THF, 22 °C, 25–41 h, **15**: ~100%, **17**: 95%; j) $NaIO_4$ (1.1–1.3 equiv), 1,4-dioxane–H_2O (3:1), 22 °C, 6–48 h; k) $NaBH_4$ (2–3.7 equiv), MeOH, 0 °C, 1–2 h, **18**: 99% (2 steps), **19**: 96% (2 steps); l) $PhB(OH)_2$ (1 equiv), PhH, reflux with Dean–Stark trap, 2.5–4.5 h, **20**: 95%, **21**: 98%

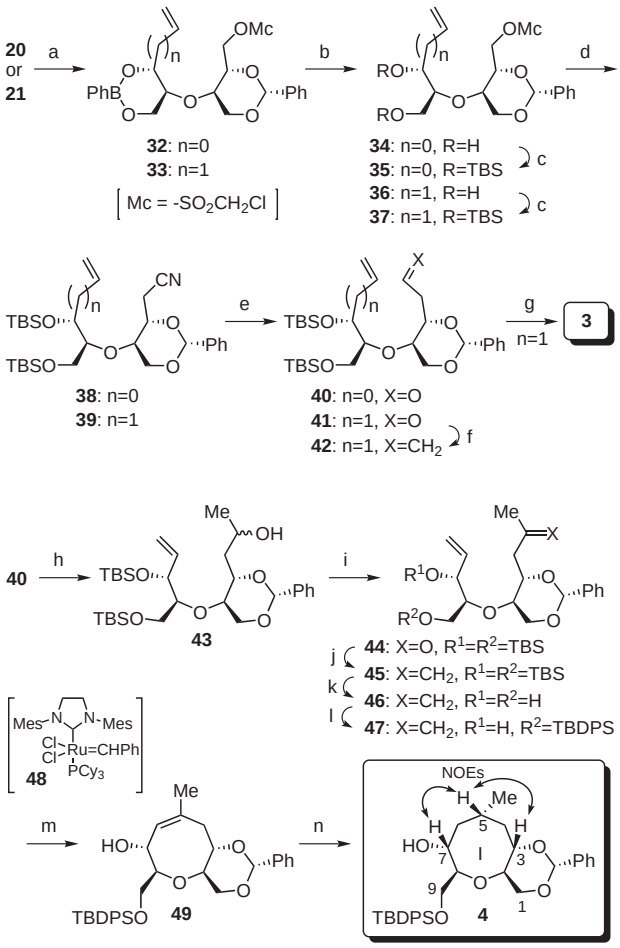


Scheme 3 Reagents and conditions. a) TPAP (0.06 equiv), NMO (1.5 equiv), MS 4Å, CH_2Cl_2, 12 min; b) Ph_3PCH_3Br (10 equiv), NaHMDS (10 equiv), THF, 22 °C, 1 h, then **22**, –78 →22 °C, 9 h, 46% for 2 steps; c) 30% H_2O_2, EtOAc, 20 °C, 1 h, 84%; d) PivCl (1.1 equiv), pyridine, 25 °C, 2.5 h, 80%; e) $(Cy_3P)_2Cl_2Ru$=CH_2Ph (0.05 equiv), $ClCH_2CH_2Cl$ (5 mM of **25**), reflux, 4 h, 90%; f) AcCl (1.1 equiv), pyridine (2.2 equiv), CH_2Cl_2, 25 °C, 1 h, ~100%; g) 30% H_2O_2, EtOAc, 20 °C, 6 h, 92%; h) TBSOTf (2.6 equiv), 2,6-lutidine (5.2 equiv), CH_2Cl_2, 25 °C, 18 h, ~100%; i) DIBALH (1 equiv), CH_2Cl_2, –78 °C, 8 min, ~100%; j) $(COCl)_2$ (3 equiv), DMSO (4.8 equiv), CH_2Cl_2, –78 °C, 20 min, then Et_3N (10 equiv), –20 °C, 5 min; k) Ph_3PCH_3Br (2 equiv), NaHMDS (2 equiv), THF, 25 °C, 1 h, then **30**, –78 °C, 6 min, 83% for 2 steps; l) TBAF (2.1 equiv), THF, 25 °C, 2 h, ~100%

lic boronate part],[14] though the instability of cyclic boronate part caused the low yield (39% overall). Since **24** is not a good precursor for RCM reaction, the primary hydroxy group was protected as pivaloate ester. The resulting **25** was readily cyclized with $(Cy_3P)_2Cl_2Ru$=CH_2Ph[15] to produce **2**[16] in 80% yield. Next, we also explored an alternative route to **24** in order to avoid the trouble owing to instability of the cyclic boronate group. Protection of alcohol **20** with acetyl group and subsequent removal of cyclic boronate afforded diol **27**, which was protected with TBS group and hydrolyzed to give **29**. Alcohol **29** was converted to diene **24** by Swern oxidation[17] followed by Wittig olefination and desilylation. The D/E-ring part **2** was eventually obtained from **20** in 26% total yield in 5 steps via **23** and in 51% total yield in 9 steps via **31**.

The I- and F-ring parts were synthesized from the corresponding substrates **20** and **21** (Scheme 4). Conversion of hydroxy group in **20** or **21** to chloromethanesulfonate ester[18] followed by a 3-step transformation [(i) removal of cyclic boronate,[14] (ii) protection with TBS, and (iii) substitution with cyanide] gave the corresponding nitrile **38** or **39**. For the F-ring construction, the nitrile group of **39** was reduced with DIBALH to an aldehyde, which was subjected to Wittig olefination to produce diene **42**. The diene **42** was transformed into the F-ring part **3**[19] in 98% yield by the RCM reaction with $(Cy_3P)_2Cl_2Ru$=CH_2Ph.[15] On the other hand, **38** was reduced to aldehyde **40**, which was subjected to addition of MeMgBr followed by oxidation to give ketone **44**. Treatment of **44** with Tebbe reagent[20] and the subsequent deprotection and protection process produced dienes **45**–**47**. After several endeavors using these dienes, we found that the RCM reaction of diene **47** with Grubbs' second generation catalyst **48**[21] in CH_2Cl_2 (5 mM of **47**) under refluxed conditions afforded cyclized compound **49** in 97% yield.[7] Stereoselective reduction of **49** was achieved only by homogeneous hydrogenation conditions using Crabtree's catalyst[22] to give the I ring part **4**[23] in 88% yield (dr 19:1). Stereochemistry of C5 was confirmed by the existence of NOEs between H5/H3 and between H5/H7 in NOESY of **4**. It is noted that this step showed unusual face selectivity which did not result from the coordination of the catalyst with the allylic hydroxy group of **49**.[22b] Interestingly, hydrogenation of **49** under heterogeneous conditions using PtO_2 gave the opposite selectivity (50% yield, dr 1:8).

Thus, chiral medium-sized monocyclic ethers corresponding to the D-, E-, F-, and I-ring parts of ciguatoxin have been synthesized from tri-*O*-acetyl-D-glucal through a common synthetic route involving ring-closing olefin metathesis. Further studies toward the total synthesis of **1** are currently under way in this laboratory.



Scheme 4 Reagents and conditions. a) $ClCH_2SO_2Cl$ (1–1.5 equiv), 2,6-lutidine (2–3 equiv), CH_2Cl_2, 21–23 °C, 2–2.5 h, **32**: ~100%, **33**: 98%; b) 30% H_2O_2, EtOAc, 21–23 °C, 2 h; c) TBSOTf (3–4.3 equiv), 2,6-lutidine (6–10 equiv), CH_2Cl_2, 21–25 °C, 2–7 h, **35**: 97% from **32**, **37**: 88% from **33**; d) KCN (6 equiv), DMSO, 23–25 °C, 12–15 h, **38**: 95%, **39**: 96%; e) DIBALH (1 equiv), CH_2Cl_2, –78 °C, 30–40 min, **40**: 97%, **41**: 88%; f) Ph_3PCH_3Br (5 equiv), NaHMDS (4.8 equiv), THF, 22 °C, 2 h, then **41**, –78 °C →23 °C, 4 h, 99%; g) $(Cy_3P)_2Cl_2Ru{=}CH_2Ph$ (0.16 equiv), CH_2Cl_2 (3 mM of **42**), reflux, 3 h, 98%; h) MeMgBr (2 equiv), Et_2O, 0 °C, 1.5 h, 89%; i) DMPI (2 equiv), $NaHCO_3$ (2 equiv), CH_2Cl_2, 0 →23 °C, 1 h, ~100%; j) Tebbe reagent (5 equiv), THF, 0 °C, 5 min, 88%; k) TBAF (3.5 equiv), THF, 23 °C, 14 h, ~100%; l) TBDPSCl (2 equiv), imidazole (6 equiv), DMF, 23 °C, 17 h, 77%; m) **48** (0.1 equiv), CH_2Cl_2 (5 mM of **47**), reflux, 4 h, 97%; n) H_2, $[(cod)(py)(Cy_3P)Ir]PF_6$ (0.3 equiv), CH_2Cl_2, –20 °C, 4.5 h, 88% (dr 19:1)

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(16) Representative data for **2**: a colorless oil; $[\alpha]_D^{22}$ +23.3 (*c*, 0.06, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$), δ 7.48 (2 H, m, Ph), 7.36 (3 H, m, Ph), 5.77 (2 H, m, H4, H5), 5.30 (1 H, s, acetal), 4.53 (1 H, dd, *J* = 12, 4.3 Hz, H8a), 4.31–4.17 (4 H, m, H1eq, H3, H6, H8b), 3.64 (1 H, t, *J* = 10 Hz, H1ax), 3.60–3.56 (1 H, m, H7), 3.52 (1 H, dt, *J* = 10, 4.8 Hz, H2), 2.92 (1 H, d, *J* = 5.7 Hz, 6-OH), 1.24 (9 H, s, *t*-Bu); IR (film): 3487, 2971, 2860, 1729, 1481, 1456, 1399, 1287, 1167, 1115, 1032, 977, 752, 698 cm^{-1}; HR-EIMS, calcd for $C_{20}H_{26}O_6$ $(M)^+$: 362.1729, found: 362.1722.

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(19) Representative data for **3**: a colorless oil; $[\alpha]_D^{21}$ –9.2 (*c* 0.29, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 55 °C), δ 7.28–7.48 (5 H, m, Ph), 5.74–5.82 (2 H, m, H5, H6), 5.40 (1 H, s, acetal), 4.52 (1 H, dd, *J* = 4.3, 10.3 Hz, H1eq), 3.77 (1 H, dd, *J* = 1.8, 10.6 Hz, H10a), 3.62–3.70 (2 H, m, H3, H8), 3.57 (1 H, dt, *J* = 4.3, 10.3 Hz, H2), 3.50 (1 H, t, *J* = 10.3 Hz, H1ax), 3.44 (1 H, dd, *J* = 7.7, 10.6 Hz, H10b), 3.32 (1 H, dt, *J* = 1.8, 7.7 Hz, H9), 2.68–2.80 (1 H, m, H4a), 2.44–2.58 (2 H, m, H7a, H4b), 2.28–2.43 (1 H, m, H7b), 0.91 (9 H, s, TBS), 0.90 (9 H, s, TBS), 0.098 (3 H, s, TBS), 0.070 (3 H, s, TBS), 0.066 (3 H, s, TBS), 0.049 (3 H, s, TBS); IR(film): 2955, 2928, 2856, 1471, 1462, 1389, 1361, 1294, 1258, 1213, 1148, 1103, 1027, 977, 836, 811, 776, 747, 665 cm^{-1}; HR-FDMS, calcd for $C_{29}H_{51}O_5Si_2$ $(M + H)^+$: 535.3298, found: 535.3275.

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(23) Representative data for **4**: a colorless oil; $[\alpha]_D^{25}$ +13.3 (*c* 0.15, $CHCl_3$); ^{1}H NMR [400 MHz, C_6D_6–$CDCl_3$ (1:1)], δ 7.66–7.72 (4 H, m, Ph), 7.51–7.47 (2 H, m, Ph), 7.33–7.15 (9 H, m, Ph), 5.29 (1 H, s, acetal), 4.08–4.17 (1 H, m, H1eq), 3.75 (1 H, dd, *J* = 10.5, 5.4 Hz, H9a), 3.69 (1 H, dd, *J* = 10.5, 5.9 Hz, H9b), 3.50–3.59 (1 H, m, H7), 3.42–3.50 (1 H, m, H3), 3.35–3.41 (2 H, m, H1ax, H2), 3.26 (1 H, brdt, *J* = 8.9, 5.5 Hz, H8), 2.28 (1 H, m, 7-OH), 1.91 (1 H, brdd, *J* = 13.8, 3.5 Hz, H4a), 1.62–1.64 (1 H, m, H5), 1.53–1.62 (3 H, m, H4b, H6), 1.09 (9 H, s, *t*-Bu), 1.00 (3 H, d, *J* = 7.1 Hz, 5-Me); IR(film): 3490, 3071, 3047, 2928, 2857, 1589, 1455, 1428, 1391, 1372, 1292, 1215, 1112, 1029, 916, 823, 744, 701, 615 cm^{-1}; HR-EIMS, calcd for $C_{29}H_{33}O_5Si$ $(M - t\text{-Bu})^+$: 489.2097, found: 489.2105.