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A very short route to the functionalized A-ring moiety of ciguatoxin

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Abstract

The functionalized AB-ring moiety of ciguatoxin has been synthesized in a highly convergent manner via transition metal catalysis.

Keywords: ciguatoxin; coupling reaction; transition metal catalysis; olefin metathesis.

Ciguatoxin (CTX1B, **1**) is the principal toxin of 'ciguatera' sea-food poisoning.[1] Every year, more than 20 000 people in the tropics and subtropics suffer from ciguatera which causes gastro-intestinal, neurological, and cardiovascular disorders.[2] The extremely limited availability of **1** (0.35 mg of **1** from 4000 kg of moray eels)[1a] has hampered further pharmacological studies and development of an immunoassay system for detecting poisonous fish.[3] The total synthesis of **1** is one of the most challenging targets in modern organic synthesis.[4] The structural features of **1** which distinguish it from other *trans*-fused polyether marine toxins[5] such as the brevetoxins include the acid-sensitive A-ring structure possessing a 1-butene-3,4-diol side-chain, which makes **1** the most potent among the congeners.[6] While several synthetic efforts to construct the A-ring of **1** have been reported, most of these syntheses are linear and lengthy.[7] Connecting the side-chain fragment (**2**) with the core (**3**) at C4–C5 should be the most convergent approach (Scheme 1).[8] However, it has not yet been realized. This approach would facilitate the total synthesis of **1** because it should allow us to construct such a labile system in the later stages of the total synthesis. We report herein an efficient methodology to synthesize the A-ring moiety of **1** in a highly convergent manner.

We first attempted a Heck coupling reaction of vinyl iodide (**2**) and cyclic enol ether (**6**) (Scheme 2). The synthesis of **6** commenced with **4**, which is available from tri-*O*-benzyl-D-glucal in two steps.[9] Allylation of the secondary alcohol (**4**) followed by the ruthenium-catalyzed ring-closing metathesis reaction gave allylic ether (**5**) in good yield. Isomerization of **5** to the cyclic enol ether (**6**) was achieved using Wilkinson's catalyst in 55% yield.[10] The Heck reaction of **6** with **2**[11] was performed under Larock's

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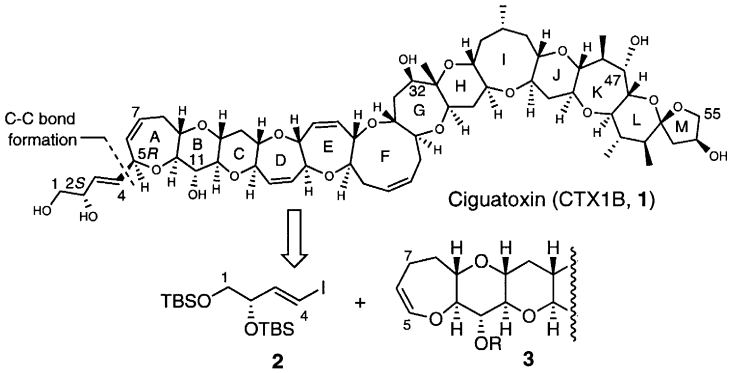
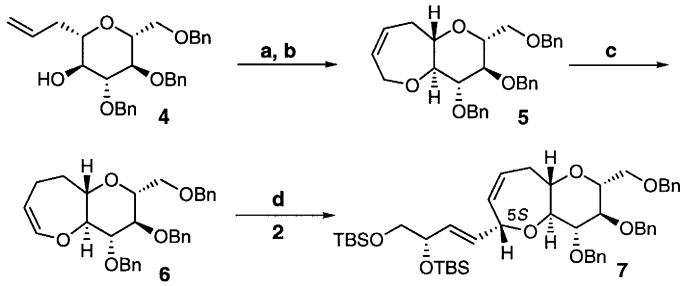


Scheme 1.

conditions[12] at 80°C. However, the undesired C5-epimer (**7**) was obtained predominantly in only low yield (10% yield based on **2**). Neither the utilization of Jeffery's conditions [cat. $Pd(OAc)_2$, n-Bu_4NCl, and KOAc in DMF at 40°C][13] nor the use of BINAP as a chiral phosphine ligand[14] gave the desired 5*R*-isomer.

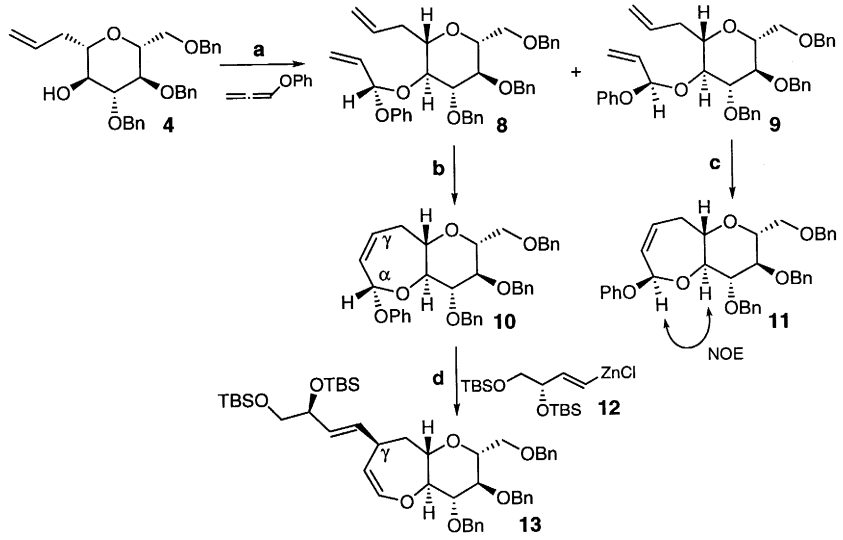


Scheme 2. Reagents and conditions: (a) allylbromide, KH, THF, 0°C to rt, 90%; (b) $Cl_2(PCy_3)_2Ru{=}CHPh$ (5 mol%), CH_2Cl_2, rt, 95%; (c) $(PPh_3)_3RhCl$ (10 mol%), DABCO (30 mol%), EtOH:H_2O (9:1), reflux, 55%; (d) **2** (0.2 equiv.), $Pd(OAc)_2$ (3 mol%), PPh_3 (9 mol%), Ag_2CO_3 (2 equiv.), CH_3CN, 80°C, **7** (10%)

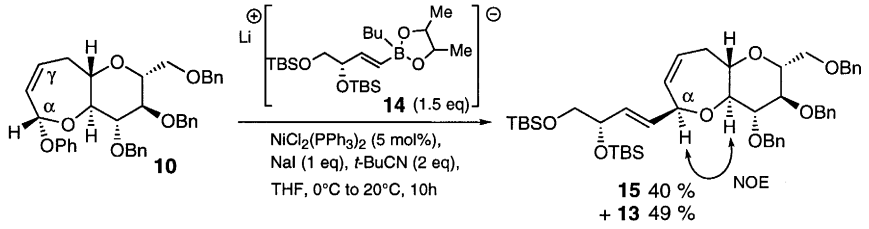
We next examined a palladium-catalyzed coupling reaction of the allylic acetal (**10**) with the vinyl metal species (**12**) (Scheme 3).[15] The secondary alcohol (**4**) was reacted with 1-phenoxy-1,2-propadiene[16] according to the Rutjes's procedure[17] to yield a mixture of allylic acetals, **8** and **9**, in 53% and 17% yields, respectively. After separation, ring-closing olefin metathesis reactions of **8** and **9** yielded **10**[18] and **11**, respectively, in good yields. The C5 stereochemistry was determined by NOE experiments. Palladium-catalyzed coupling of **10** with **12**,[19] however, yielded a γ-adduct (**13**) selectively.

This problem was solved by applying Kobayashi's nickel-catalyzed reaction (Scheme 4).[20] The coupling of **10** with borate (**14**)[21] was conducted in the presence of $NiCl_2(PPh_3)_2$ (10 mol%), NaI (1 equiv.), and *t*-BuCN (2 equiv.) in THF. The reaction proceeded smoothly below room temperature to give **15**[22] and the regioisomer (**13**) in 40% and 49% yields, respectively.[23] The C5 stereochemistry of **15** was confirmed by NOE experiments.

Thus, we succeeded in the synthesis of the AB-ring moiety (**15**) of **1** in only three steps from the D-glucose derivative (**4**). The present methodology should provide an extremely expeditious entry to construct the labile A-ring system of **1**. Further efforts directed towards the total synthesis of ciguatoxin (**1**) are currently underway in our laboratory.



Scheme 3. Reagents and conditions: (a) $Pd(OAc)_2$ (5 mol%), $Ph_2P(CH_2)_3PPh_2$ (5 mol%), 1-phenoxy-1,2-propadiene (5 equiv.), Et_3N (1.5 equiv.), CH_3CN, 80°C, 9 h, **8** (53%) and **9** (17%); (b) $Cl_2(PCy_3)_2Ru{=}CHPh$ (5 mol%), CH_2Cl_2, reflux, 89%; (c) $Cl_2(PCy_3)_2Ru{=}CHPh$ (10 mol%), CH_2Cl_2, reflux, 68%; (d) **12** (1.5 equiv.), $Pd(PPh_3)_4$ (10 mol%), 0°C to 35°C, THF, **13** (70%)



Scheme 4.

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11. The fragment (**2**) was synthesized from (*R*)-1-benzyl glycerol as follows: (i) TBSCl, imidazole, DMF, 97%; (ii) $Pd(OH)_2$, H_2, 97%; (iii) Dess–Martin periodinane, CH_2Cl_2; (iv) $CrCl_2$, CHI_3, THF, 0°C to rt, 58% (two steps); synthesis of (*R*)-1-benzyl glycerol, see: Takano, S.; Goto, E.; Hirama, M.; Ogasawara, K. *Heterocycles* **1981**, *16*, 381.
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18. Compound **10**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.59 (1H, m, H8), 2.80 (1H, dt, *J*=17.5, 6.0 Hz, H8), 3.49 (1H, m, H13), 3.52 (1H, m, H9), 3.54 (1H, t, *J*=9.5 Hz, H12), 3.62 (1H, dd, *J*=10.0, 5.0 Hz, H14), 3.64 (1H, t, *J*=9.0 Hz, H11), 3.70 (1H, dd, *J*=10.5, 2.0 Hz, H14), 4.21 (1H, t, *J*=9.0 Hz, H10), 4.42 (1H, d, *J*=11.0 Hz, O*CH*$_2$Ph), 4.54 (1H, d, *J*=12.5 Hz, O*CH*$_2$Ph), 4.58 (1H, d, *J*=12.5 Hz, O*CH*$_2$Ph), 4.61 (1H, d, *J*=11.0 Hz, O*CH*$_2$Ph), 4.68 (1H, d, *J*=11.0 Hz, O*CH*$_2$Ph), 4.70 (1H, d, *J*=11.0 Hz, O*CH*$_2$Ph), 5.80 (1H, m, H6), 5.86 (1H, ddd, *J*=11.5, 6.0, 4.0 Hz, H7), 5.97 (1H, d, *J*=3.5 Hz, H5), 6.85–7.34 (20H, m); FT-IR (film) ν_{max} 3029, 2911, 2867, 1597, 1493, 1452, 1357, 1220, 1150, 1101, 1068, 1027, 991, 946, 754, 735, 697 cm^{-1}; $[\alpha]_D^{29}$ +46.3 (*c* 1.02, $CHCl_3$); ESI-MS, calcd for $C_{37}H_{38}O_6Na$ ($M+Na^+$) 601.257, found 601.253.
19. The vinyl zinc (**12**) was synthesized from **2**: *n*-BuLi (1.5 equiv.) in THF at −78°C for 2 h; then $ZnCl_2$ (1.2 equiv.) from −78°C to 0°C.
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21. The borate (**14**) was prepared from **2** as follows: (i) *n*-BuLi (1.5 equiv.), THF, −78°C, 2 h, then $B[OCH(CH_3)_2]_3$ (1.5 equiv.), −78°C to rt, then NH_4Cl; (ii) 2,3-butanediol, $MgSO_4$, toluene, rt, 69% (two steps); (iii) *n*-BuLi (1.1 equiv.), THF, 0°C, 15 min.
22. Compound **15**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.02 (6H, s), 0.03 (3H, s), 0.05 (3H, s), 0.87 (9H, s) 0.88 (9H, s) 2.46 (1H, m, H8), 2.70 (1H, m, H8), 3.26 (1H, td, *J*=9.5, 3.5 Hz, H9), 3.43 (1H, dd, *J*=10.5, 5.5 Hz, H1), 3.46 (1H, dd, *J*=10.5, 4.0 Hz, H1), 3.48 (1H, m, H13), 3.54 (1H, t, *J*=9.5 Hz, H12), 3.57 (1H, t, *J*=9.5 Hz, H10), 3.62 (1H, dd, *J*=10.5, 5.5 Hz, H14), 3.68 (1H, t, *J*=9.5 Hz, H11), 3.70 (1H, dd, *J*=10.5, 1.5 Hz, H14), 4.17 (1H, m, H2), 4.49 (1H, d, *J*=10.5 Hz, O*CH*$_2$Ph), 4.54 (1H, d, *J*=12.0 Hz, O*CH*$_2$Ph), 4.57 (1H, d, *J*=12.0 Hz, O*CH*$_2$Ph), 4.62 (1H, m, H5), 4.75 (1H, d, *J*=10.5 Hz, O*CH*$_2$Ph), 4.83 (1H, d, *J*=10.5 Hz, O*CH*$_2$Ph), 5.00 (1H, d, *J*=10.5 Hz, O*CH*$_2$Ph), 5.77–5.83 (3H, m, H3, H6, H7), 5.87 (1H, dd, *J*=15.5, 5.0 Hz, H4), 7.10–7.40 (15H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.37, −5.27, −4.65, −4.64, 18.29, 18.38, 25.72, 25.88, 25.97, 34.15, 68.07, 69.25, 73.45, 73.54, 75.01, 75.46, 75.71, 77.83, 78.05, 78.46, 85.43, 87.32, 115.28, 120.70, 127.24, 127.53, 127.59, 127.65, 127.74, 127.84, 127.90, 127.97, 128.11, 128.34, 129.63, 130.61, 131.35, 135.50, 138.12, 138.26, 138.82; FT-IR (film) ν_{max} 2955, 2928, 2857, 1471, 1361, 1255, 1102, 1028, 970, 835, 777, 734, 697 cm^{-1}; $[\alpha]_D^{28}$ +20.3 (*c* 0.776, $CHCl_3$); MALDI-TOF-MS, calcd for $C_{47}H_{68}O_7Na$ ($M+Na^+$) 823.440, found 823.462.
23. The phenoxy group in **10** as a leaving group was crucial to attain **15**. A similar reaction of the corresponding methyl acetal with **14** did not proceed at room temperature; the tetrahydrooxepin ring opening occurred when heated.[24]
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