A Short Synthesis of the A/B Ring Systems of the Pacific Ciguatoxins P-CTX-3C and Dihydroxy-P-CTX-3C

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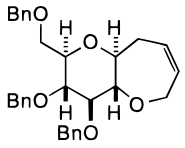
The discovery and subsequent structural elucidation of the Pacific ciguatoxin P-CTX-3C was first reported in 1993.[1] Very recently Yasumoto's group reported the isolation and characterization of the closely related dihydroxy-P-CTX-3C.[2] Each of these toxins consists of 13 contiguous, fused cyclic ethers ranging in size from six to nine members. Their structures are shown in Figure 1.

As consumption of ciguateric fish (i.e., those fish which have accumulated ciguatoxins in their flesh as a result of ingesting *Gambierdiscus toxicus*, a benthic dinoflagellate which synthesizes these toxins[3]) can cause ciguatera in humans, there is a need to develop a simple assay for the presence of these toxins in fish. Because of the very low concentrations (<0.1 ppb) of ciguatoxins in fish such an assay will need to be highly sensitive, such as an immunoassay.[4] One approach to developing such a test is to synthesize in enantiomerically pure form two to four rings at each end of the ciguatoxin molecule. With these in hand a sandwich-type immunoassay can then be developed for the different ciguatoxins.[4] Hence, as part of a program directed toward the synthesis of the terminal domains of the Pacific ciguatoxins P-CTX-3C, and 2,3-dihydroxy-P-CTX-3C we report in this Note the first synthesis of their A/B terminal ring systems (**1** and **2**, respectively).



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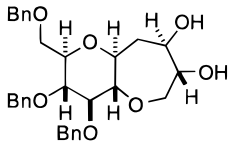

2

The synthesis of the initial target **1** is outlined in Scheme 1; the sequence from **4** to **6** is based on a sequence (steps ii−v) involving Kishi's stereoselective reductive allylation of tetra-*O*-benzyl-D-gluconolactone (**4**)[5] followed by Nicotra's two-step protocol for the selective deprotection of the C2-benzyl ether to give **5**.[6] This sequence proceeded satisfactorily in our hands. However, the simple oxidation of commercially available **3** to give lactone **4** using PDC was somewhat disappointing. Yields were improved by the use of TPAP/NMO[7] which gave virtually quantitative yields of pure **4** in approximately 30 min. This procedure was amenable to reasonable scale-up to 10 g scale.

Ring-closing metathesis[8−17] of the corresponding *O*-allyl derivative **7**[18] then provided **1** in excellent yield as a single regioisomer. Our first attempts to *trans*-dihydroxylate **1** using aqueous 3-chloroperbenzoic acid[19] gave a modest yield of a separable, 5:1 mixture of the two isomeric epoxides **8** and **9** (Scheme 2).

An X-ray crystal structure was obtained for the major isomer which showed it to be the α-epoxide **8** as shown in Figure 2. Simple epoxidation using 3-chloroperbenzoic acid in dichloromethane gave an improved (12:1) ratio of epoxides **8** and **9** in 65% total yield.

Treatment of **8** with aqueous sulfuric acid at room tempereature overnight led to a 1:1 mixture of the desired 2,3-*trans*-diol **10** along with its 2,3-bis-epimer **11**. The relative stereochemistries of **10** and **11** were established by NOE experiments (Scheme 3). Studies intended to improve the selectivity of the ring opening of epoxides such as **8** as well as the extension of this chemistry to the synthesis of other ciguatoxin domains are underway in our laboratories.

In conclusion simple, straightforward syntheses of the AB terminal rings of 2*R*,3*R*-dihydroxy-P-CTX-3C and P-CTX-3C have been developed. Key steps involved: (i) the Kishi−Nicotra conversion of tetra-*O*-benzyl-D-gluconolactone into the *β*-glycoside **6**; (ii) ring-closing metathesis of the *O*-allyl derivative **7**; (iii) a two-step *trans*-dihydroxylation of **1**.

Experimental Section

General Methods. All reactions were conducted under a nitrogen atmosphere. Flash chromatography was carried out using silica gel (230−400 mesh). Melting points were measured on a hot stage melting point apparatus and are uncorrected. ^{1}H

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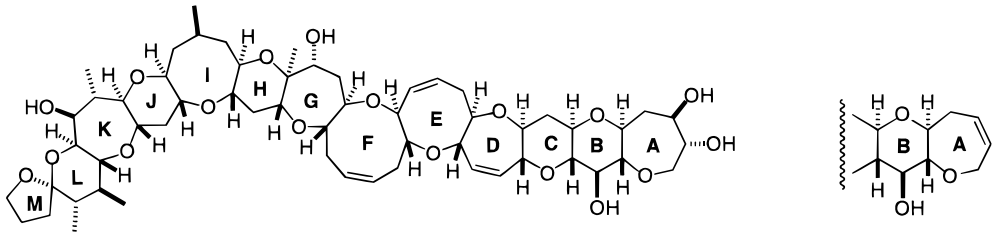
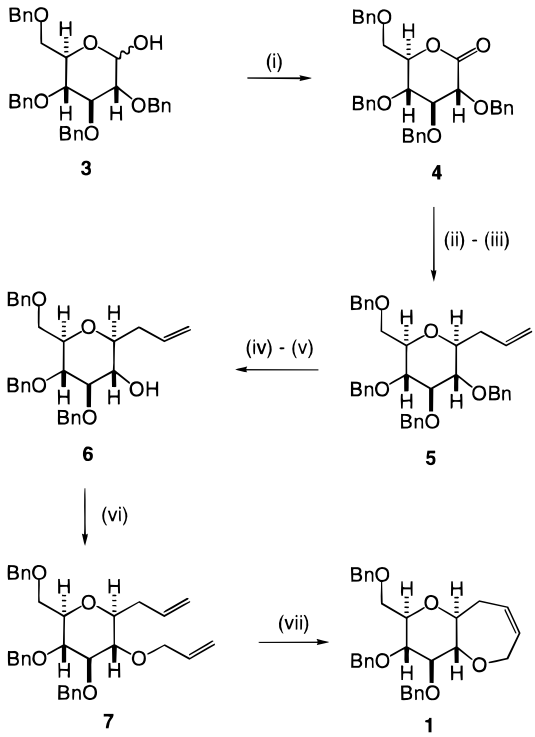


2R,3R-Dihydroxy-P-CTX-3C P-CTX-3C

Figure 1.

Scheme 1



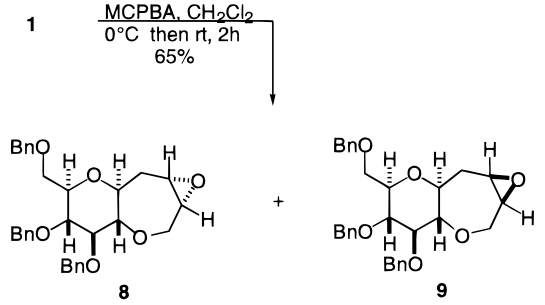
(i) TPAP, NMO, CH_3CN, 95%; (ii−iii) ref 5; (iv−v) ref 6; (vi) (a) NaH, DMF, (b) $CH_2{=}CHCH_2Br$, 87%; (vii) $(Cy_3P)_2RuCl_2(CHPh)$, toluene, rt, o/n, 81%.

Figure 2. X-ray structure of **8** (some hydrogens omitted for clarity).

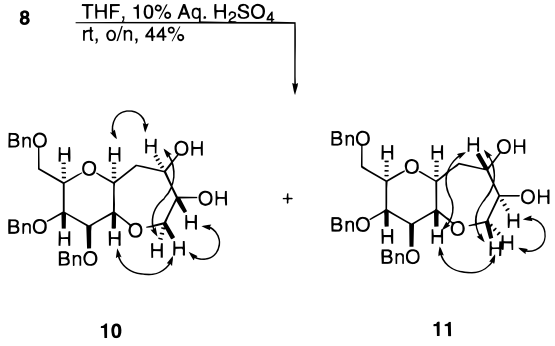
NMR spectra were recorded at 300, 400, and 500 MHz in $CDCl_3$. ^{13}C NMR spectra were recorded at 75 or 100 MHz in $CDCl_3$.

2,3,4,6-Tetra-*O*-benzylgluconolactone (4). Solid TPAP (tetrapropylammonium perruthenate)[7] (160 mg, 0.46 mmol, 5 mol %) was added in one portion to a stirred mixture of **3** (5 g, 9.2 mmol, 1 equiv), *N*-methylmorpholine *N*-oxide (NMO) (1.62 g, 13.8 mmol, 1.5 equiv), and powdered 4 Å molecular sieves (4.6 g, 500 mg/mmol) in acetonitrile (40−60 mL) at room temperature under a dry nitrogen atmosphere. The reaction was monitored by TLC and was complete within 0.5 h after which time the reaction mixture was concentated in vacuo, diluted with dichloromethane, filtered through a pad of silica and concentrated to give 4.74 g (95%) of the pure lactone[5] as a colorless oil.

Scheme 2



Scheme 3



3-(2′-*O*-Prop-1″-enyl-3′,4′, 6′-tri-*O*-benzyl-*β*-D-glucopyranosyl)prop-1-ene (7). A suspension of **6**[6] (474 mg, 1 mmol) and NaH (36 mg, 1.2 mmol, 80% in mineral oil) in DMF (7.5 mL) was stirred under an atmosphere of argon for 80 min, and then allyl bromide (104 μL, 145 mg, 1.2 mmol) was added. After a further 2 h, more NaH (36 mg) was added as there was still some starting material as shown by TLC. After another 2 h, the reaction was quenched with saturated aqueous sodium chloride, diluted with EtOAc, washed with water, extracted with ether, and dried ($MgSO_4$) to give a crude yield of 497 mg (97%) of a yellow oil. Following purification by column chromatography (15% EtOAc/petroleum ether), **7** was obtained as a colorless oil (448 mg, 87%). $[\alpha]^{28}_D$ +1.3 (*c*, 1.1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 2.26 (dddt, *J* 14.6, *J* 7.3, *J* 7.3, *J* 1.1 Hz, 1H), 2.53 (dddt, *J* 14.6, *J* 6.4, *J* 3.3, *J* 1.7 Hz, 1H), 3.13 dd (*J* 9.5, *J* 8.7 Hz, 1H), 3.25 (ddd, *J* 9.5, *J* 7.3, *J* 3.3 Hz, 1H), 3.35 (ddd, *J* 9.4, *J* 4.4, *J* 2.1 Hz, 1H), 3.51 (dd *J* 9.4, *J* 9.1 Hz, 1H), 3.58 (dd, *J* 9.1, *J* 8.7 Hz, 1H), 3.62 (dd, *J* 11.0, *J* 4.4 Hz, 1H), 3.67 (dd, *J* 11.0, *J* 2.1 Hz, 1H), 4.09 (ddt, *J* 12.2, *J* 5.6, *J* 1.4, 1H), 4.29. ddt (*J* 12.2, *J* 5.6, *J* 1.4, 1H), 4.50,4.57 (ABq, *J* 12.6 Hz, 2H), 4.52, 4.76 (ABq, *J* 10.8 Hz, 2H), 4.81 (s, 2H), 5.01−5.22 (m, 4H), 5.81−5.94 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.1, 69.1, 73.4, 74.0, 74.9, 75.5, 78.6, 78.8, 79.1, 81.6, 87.2, 116.9, 117.0, 127.7, 127.7, 127.8, 127.9, 128.3, 128.4, 134.9, 134.9, 138.3, 138.4, 138.7. IR (film) 1643, 1606 cm^{-1}. HRMS *m/e* calcd for $C_{33}H_{38}O_5Na$ (M + Na^+): 537.262, found 537.261.

(2*R*,3*R*,4*S*,4a*S*,9a*S*)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-2,3,4,4a,9,9a-hexahydro-6*H*-pyrano[3,2-*b*]oxepin (1). Bis-

(tricyclohexylphosphine)benzylidene ruthenium(IV) dichloride (7 mg, 8.5 μmol, 4 mol %) was added to a stirred solution of **7** (100 mg, 0.2 mmol) in toluene (5 mL) under an atmosphere of argon. The reaction color changed from a pink-purple to a clear brownish solution. The reaction was left to stir overnight at room temperature and then filtered through a pad of Celite and concentrated in vacuo. Purification by flash chromatography (10%EtOAc/petroleum ether) gave **1** as a colorless oil (77 mg, 81%). $[\alpha]^{28}_D$ +12.5 (*c*, 1.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.39−2.50 (m, 1H), 2.72 (ddd, *J* 16.2, 8.0, 4.0 Hz, 1H), 3.27 ddd (*J* 10, *J* 9.3, *J* 4.0 Hz, 1H), 3.44 (dd, *J* 9.3, *J* 8.4 Hz, 1H), 3.47 (ddd, *J* 9.5, *J* 4.6, *J* 1.9 Hz, 1H), 3.58 (dd *J* 9.5, *J* 8.7 Hz, 1H), 3.65 (dd, *J* 10.6, *J* 4.6 Hz, 1H), 3.66 (dd, *J* 8.7, *J* 8.4 Hz, 1H), 4.00 (ddd, *J* 15.2, *J* 5.3 *J* 2.5 Hz, 1H), 4.30 (dd, *J* 15.2, *J* 5.9, 1H), 4.56, 4.62, (ABq, *J* 12.2 Hz, 2H), 4.52, 4.86 (ABq, *J* 10.7 Hz, 2H), 4.82, 4.98 (ABq, *J* 11.2 Hz, 2H), 5.82 (dddd, *J* 4 11.4, *J* 8.0, *J* 3 0.4, *J* 2.5 Hz, 1H), 5.92 (dddd, *J* 11.4, *J* 5.9, *J* 3.6, 3.0 Hz, 1H), 7.14−7.42 (m, 15H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.6, 67.8, 69.3, 73.5, 75.0, 75.6, 76.0, 77.8, 78.4, 85.8, 88.1, 127.4, 127.5, 127.4, 127.6, 127.7, 127.9, 128.0, 128.3, 128.3, 131.5, 138.2, 138.4, 139.1. MS *m*/*z* 487.4 (M + H^+), 509.4 (M + Na^+), 525.3 (M + K^+). IR (film) 1606 cm^{-1}. HRMS *m*/*e* calcd for $C_{31}H_{34}O_5Na$ (M + Na^+): 509.230, found 509.231.

(2*R*,3*R*,4*S*,4a*S*,7*R*,8*R*,9a*S*)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-2,3,4,4a,7,8,9,9a-octahydro-6*H*-pyrano[3,2-*b*]oxepin-7,8-epoxide (8) and (2*R*,3*R*,4*S*,4a*S*,7*S*,8*S*,9a*S*)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-2,3,4,4a,7,8,9,9a-octahydro-6*H*-pyrano[3,2-*b*]oxepin-7,8-epoxide (9). A solution of oxepin **1** (300 mg, 0.62 mmol) in dichloromethane (12 mL) was cooled to 0 °C and *m*CPBA (500 mg, 2.47 mmol, 85% pure) was added slowly. The reaction mixture was maintained at 0 °C, and then warmed to ambient temperature and stirred for 2 h. Solid NaOH (1 pellet) was then added to the reaction mixture. This mixture was diluted with saturated aqueous NaCl (20 mL) and extracted with ethyl acetate (3 × 20 mL). The organic extract was dried (CaO) and the crude material purified by preparative chromatography (ethyl acetate/light petroleum) providing the epoxides **8** and **9** (total mass of 186 mg) in 60% and 5% yields, respectively. **8**: mp 103−106 °C. $[\alpha]^{28}_D$ +5.6 (*c* 0.8, $CHCl_3$). IR (Nujol) 1497, 1453, 1360, 1105, 1073, 1028, 912, 749, 697, 668 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.06 (dd, *J* 15.3, 10.9 Hz, 1H), 2.83 (dt, *J* 15.3, 4.6 Hz, 1H), 2.96 (dd, *J* 9.2, 8.4 Hz, 1H), 3.04 (dd, *J* 4.2, 3.0 Hz, 1H), 3.22 (t, *J* 4.6 Hz, 1H), 3.36−3.45 (m, 2H), 3.50 (dd, *J* 9.4, 9.1 Hz, 1H), 3.59 (dd, *J* 9.0, 8.4 Hz, 1H), 3.63 (dd, *J* 10.8, 4.5 Hz, 1H), 3.69 (dd, *J* 10.8, 2.0 Hz, 1H), 3.79 (d, *J* 14.3 Hz, 1H), 4.41 (dd, *J* 14.3, 3.1 Hz, 1H), 4.50 and 4.81 (ABq, *J* 10.8 Hz, 2H), 4.52 and 4.59 (ABq, *J* 12.2 Hz, 2H), 4.79 and 4.90 (ABq, *J* 11.2 Hz, 2H), 7.12−7.37 (m, 15H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$) δ 33.7, 52.6, 55.5, 66.3, 69.0, 73.5, 75.0, 75.2, 75.8, 77.2, 78.1, 85.6, 86.9, 127.4, 127.5, 127.5, 127.7, 127.7, 127.8, 128.2, 137.9, 138.1, 138.9. HRMS *m*/*e* calcd for $C_{31}H_{34}O_6Na$ (M + Na^+): 525.225, found 525.222. **9**: oil. [α]S(28,D) +12.7 (*c* 0.45, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.83 (ddd, *J* 14.0, 11.9, 7.1 Hz, 1H), 2.64 (ddd, *J* 14.0, 7.0, 2.0 Hz, 1H), 3.12−3.15 (m, 1H), 3.21−3.27 (m, 3H), 3.30−3.34 (m, 1H), 3.44−3.46 (m, 1H), 3.49 (dd, *J* 9.8, 8.6 Hz, 1H), 3.57−3.62 (m, 2H), 3.68 (app d, *J* 10.5 Hz, 1H), 4.47−4.49 (m, 1H), 4.47 and 4.81 (ABq, *J* 10.8 Hz, 2H), 4.53 and 4.58 (ABq, *J* 12.3 Hz, 2H), 4.75 and 4.92 (ABq, *J* 11.1 Hz, 2H), 7.12−7.36 (m, 15H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.8, 50.1, 54.3, 69.1, 71.5, 73.5, 75.0, 75.1, 75.7, 77.3, 78.9, 85.2, 89.8, 127.5, 127.6, 127.7, 127.7, 127.8, 127.9, 128.3, 137.9, 138.0, 138.8. HRMS *m*/*e* calcd for $C_{31}H_{34}O_6Na$ (M + Na^+): 525.225, found 525.226.

(2*R*,3*R*,4*S*,4a*S*,7*R*,8*R*,9a*S*)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-7,8-dihydroxy-2,3,4,4a,7,8,9,9a-octahydro-6*H*-pyrano[3,2-*b*]oxepin (10) and (2*R*,3*R*,4*S*,4a*S*,7*S*,8*S*,9a*S*)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-7,8-dihydroxy-2,3,4,4a,7,8,9,9a-octahydro-6*H*-pyrano[3,2-*b*]oxepin (11). To a solution of the epoxide **8** (42 mg, 0.084 mmol) in THF (0.7 mL) was added in portions 10% aqueous H_2SO_4 (3.5 mL), and the reaction mixture was stirred overnight at room temperature. Sodium hydroxide (1 pellet) was added to the reaction mixture which was then washed with saturated aqueous sodium chloride solution (10 mL) and the aqueous phase extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were dried (CaO), filtered, and concentrated in vacuo to give a solid (23 mg). Separation of the two isomers by HPLC provided pure samples of each of the isomers. **10**: Low R_f isomer. mp 118.5−120 °C. $[\alpha]^{33}_D$−4.9 (*c* 0.41, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.62 (bs, 2H, 1.84 (dt, *J* 13.5, 10.8 Hz, 1H), 2.34 (ddd, *J* 13.5, 4.2, 2.4 Hz, 1H), 3.10−3.15 (m, 1H), 3.30 (ddd, *J* 10.8, 9.7, 4.2 Hz, 1H), 3.42−3.47 (m, 1H), 3.49−3.56 (m, 2H), 3.63 (dd, *J* 10.8, 4.5 Hz, 1H), 3.70 (dd, *J* 10.8, 2.0 Hz, 1H), 3.73 (dd, *J* 8.3, 5.8, 4.6 Hz, 1H), 3.86 (ddd, *J* 10.8, 8.3, 2.4, 1H), 3.90 (dd, *J* 13.2, 4.6 Hz, 1H), 4.01 (dd, *J* 13.2, 5.8 Hz, 1H), 4.49, 4.82 (ABq, *J* 10.7 Hz, 2H), 4.52, 4.59 (ABq, *J* 12.1 Hz, 2H), 4.77, 4.90 (ABq, *J* 11.2 Hz, 2H), 6.99−7.36 (m, 15H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 39.3, 69.0, 70.7, 73.5, 74.0, 75.1, 75.5, 75.6, 76.1, 77.6, 79.0, 85.2, 85.9, 127.6, 127.6, 127.7, 127.8, 127.9, 128.3, 137.9, 138.0, 138.7. IR ($CHCl_3$) 3522, 3376 cm^{-1}. HRMS calcd for $(C_{31}H_{36}O_7Na)^+$: *m*/*z* 543.236, found 543.236. **11**: High R_f isomer. mp 100.5−102.5 °C. $[\alpha]^{33}_D$ +8.9 (*c* 0.25, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.17 (bs, 2H), 2.20 (t, *J* 6.0 Hz, 2H), 3.28−3.34 (m, 1H), 3.43 (ddd, *J* 9.7, 4.7, 1.9 Hz, 1H), 3.47 (dd, *J* 12.6, 7.7 Hz, 1H), 3.51 (dd, *J* 3.9, 2.0 Hz, 1H), 3.52−3.56 (m, 2H), 3.63 (dd, *J* 10.8, 4.7 Hz, 1H), 3.67−3.71 (m, 1H), 3.96−4.00 (m, 1H), 4.13 (dd, *J* 12.5, 4.6 Hz, 1H), 4.49, 4.82 (ABq, *J* 10.8 Hz, 2H), 4.52, 4.59 (ABq, *J* 12.3 Hz, 2H), 4.77, 4.90 (ABq, *J* 11.1 Hz, 2H), 7.13−7.36 (m, 15H). ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 36.8, 69.3, 70.8, 72.0, 73.6, 74.3, 74.8, 75.1, 75.4, 78.0, 79.4, 84.4, 85.2, 127.7, 127.7, 127.7, 127.9, 128.4, 138.0, 138.1, 138.2. IR ($CHCl_3$) 3487, 3175 cm^{-1}. HRMS calcd for $(C_{31}H_{36}O_7Na)^+$: *m*/*z* 543.236, found 543.236.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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