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Synthesis of the common left-half part of pectenotoxins

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Abstract—The common left-half [C31–C33(OC1–C7)–C40] part of pectenotoxins has been synthesized convergently from the C31–C35, C36–C40, and C1–C7 parts. The C31–C35 part, prepared via a new route shorter than our previous route, was coupled with the C36–C40 part through reductive lithiation and addition reactions to give an adduct stereoselectively, which was converted to a cyclic acetal corresponding to the C31–C40 part. The left-half was synthesized by a three-step process including esterification of the C31–C40 part with the C1–C7 part.

The pectenotoxin (PTX) family of diarrhetic shellfish toxins, represented by pectenotoxin 2 (**1**), was isolated from toxicated scallop *Patinopecten yessoensis* and dinoflagellate *Dinophysis fortii* by the Yasumoto group.[1] All PTXs have a polyether macrolide structure including a spirocyclic acetal, a six-membered cyclic hemiacetal, a bicyclic acetal, and three oxolanes. The unusual and complex structural features of PTXs as well as their interesting bioactivity,[1a,2] such as potent cytotoxicity against cancer cells[3] and actin-depolymerizing activity,[4] have attracted the attention of synthetic chemists.[5] As part of our program aiming at total synthesis of PTXs,[6] we describe here the synthesis of the common left-half [C31–C33(OC1–C7)–C40] part (**2**) of PTXs (Scheme 1).

The left-half **2** was planned to be synthesized from C1-C7 part **4** and C31–C40 part **3** (Scheme 1). Although we have previously synthesized a similar C31–C40 part to **3** using a coupling reaction of a chiral α-lithiotetrahydrofuran,[6b] it appeared later that the chirality of the synthetic C31–C40 part was opposite to that of natural PTXs.[1c] Therefore, we intended to construct **3** from C36–C40 part **5** and C31–C35 part **6**[6b] by our established method with proper chirality.[6b]

The synthesis of **3** is illustrated in Scheme 2. First, the aldehyde **5** was prepared from the known epoxide **7**[7] (⩾95%ee). Regioselective cleavage of **7** with $AlMe_3$ gave diol **8**,[8] which was selectively converted to the aldehyde **5** through a three-step process [(i) benzylidene acetal formation, (ii) reductive acetal cleavage, and (iii) Dess–Martin oxidation[9]]. Next, an alternative short synthesis of the known **6**[6b] was examined. Homoallyl alcohol **11**,[10] readily obtainable from D-glyceraldehyde acetonide **10**,[11] was converted to **12** through protection with *p*-methoxybenzyl (PMB) chloride (99%), hydrolysis of the acetonide part, and selective protection with TBDPSCl (68% for two steps). Oxidative cleavage of the olefin part in **12** afforded cyclic hemiacetal **13** (94%), which was transformed into α-phenylthiotetrahydrofuran **6** (85%, a mixture of anomeric isomers) by acetylation and the subsequent treatment with thiophenol in the presence of $Et_2O{\cdot}BF_3$. Thus, this route could provide **6** more facilely than the previous route.[6b] The assembly of **5** and **6** was undertaken according to our procedure.[6b,12] Treatment of **6** with 2 equiv of lithium 4,4′-di-*tert*-butylbiphenylide (LDBB) at −95 °C followed by the reaction with **5** (1.8 equiv) produced alcohol **14** as a mixture of diastereomers in 71% yield. Swern oxidation[13] of **14** gave **15** (98%) as a 4.2:1 mixture of diastereomers at C35. The major diastereomer of **15** was proved to have the desired stereochemistry by detailed NMR analysis. After detachment of two PMB groups of **15** with DDQ, the desired diastereomer was isolated as a cyclic hemiacetal (70%),

Keywords: Pectenotoxin 2; Reductive coupling reaction; Natural product synthesis; Polyether macrolide.
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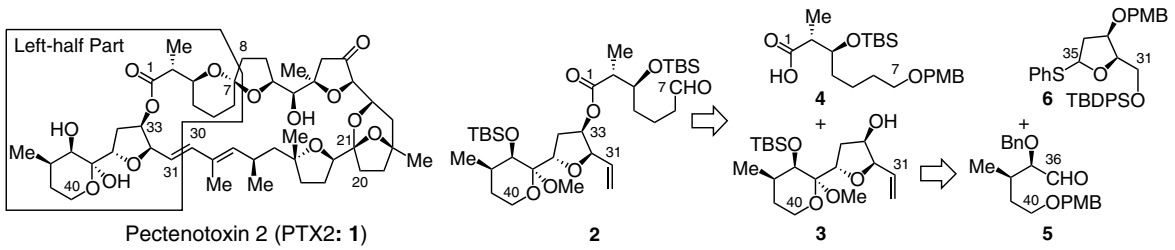
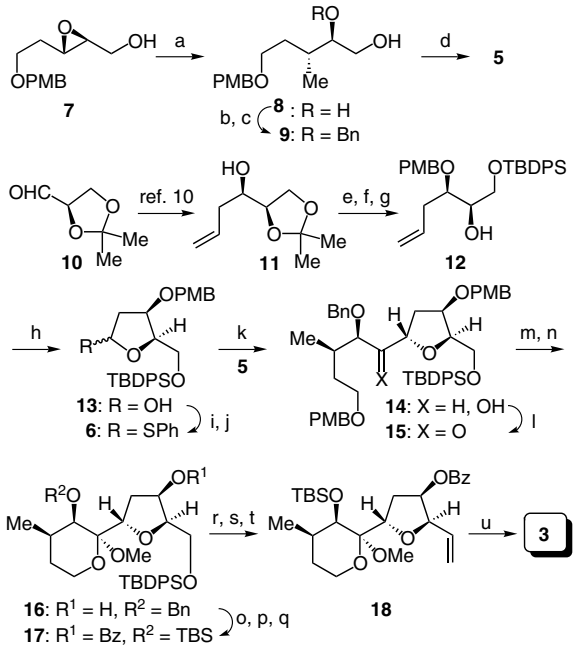


Scheme 1.



Scheme 2. Reagents and conditions: (a) Me_3Al, CH_2Cl_2, 0 °C, 2 h, 94%; (b) CSA, PhCHO, PhH, reflux, 1 h, 94%; (c) DIBALH, PhH, 0 °C, 1.5 h, 74%; (d) DMPI, $NaHCO_3$, CH_2Cl_2, 0 °C, 30 min, 97%; (e) PMBCl, NaH, Bu_4NI, DMF, 23 °C, 2 h, 99%; (f) 2 M HCl aq–THF (1:2), 23 °C, 1.5 h, 90%; (g) TBDPSCl, Et_3N, DMAP, CH_2Cl_2, 23 °C, 19 h, then separation, 76%; (h) OsO_4, NMO 1,4-dioxane–H_2O (3:1), 23 °C, 19 h, then $NaIO_4$, pH 7 buffer, 24 °C, 12 h, 94%; (i) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 24 °C, 1.5 h, 98%; (j) PhSH, $Et_2O{\cdot}BF_3$, CH_2Cl_2, −40 °C, 15 min, 87%; (k) LDBB (2 equiv), THF, −95 °C, 1 min, then **5** (1.8 equiv), −78 °C, 40 min, 71%; (l) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 10 min, then Et_3N, −78 → 0 °C, 20 min, 98%; (m) DDQ, CH_2Cl_2–H_2O (10:1), 0 °C, 1 h, then separation, 70%; (n) CSA, MeOH–$(MeO)_3CH$ (1:1), 21 °C, 2 h, 83%; (o) BzCl, DMAP, pyridine, CH_2Cl_2, 0 → 24 °C, 21 h, 100%; (p) DDQ, CH_2Cl_2-pH 7 buffer (1:1), 25 °C, 3.5 h, 86%; (q) TBSOTf, 2,6-lutidine, DMAP, CH_2Cl_2, 24 °C, 2 h, 90%; (r) TBAF, AcOH, DMF, 23 °C, 3.3 h, 88%; (s) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 10 min, then Et_3N, −78 → 0 °C, 20 min; (t) Ph_3PCH_3Br, NHMDS, THF, 23 °C, 1 h, then aldehyde, −78 → 0 °C, 1 h, 63% for two steps; (u) K_2CO_3, MeOH, 23 °C, 3.5 h, 86%.

which was stereoselectively converted to cyclic methyl acetal **16** (83%). Protection of the secondary hydroxy group of **16** as a benzoate ester followed by removal of the benzyl group with DDQ[14] and protection of the resulting alcohol with TBSOTf produced **17** (overall 77%). After the TBDPS group of **17** was selectively removed by Hashimoto's conditions[15] (88%), the resulting alcohol was subjected to oxidation followed by Wittig reaction to afford **18** (overall 63%), which was treated with K_2CO_3 in MeOH to produce **3** (86%). Since **3** was obtained as crystals (colorless needles from hexane–Et_2O, mp 131–133 °C), the stereochemistry of **3** was confirmed by X-ray crystallographic analysis (Fig. 1).[16] Thus, the C31–C40 part **3** having the proper absolute stereochemistry was concisely synthesized from **7** and **11**.

The synthesis of the C1–C7 part **4** and the left-half part **2** is shown in Scheme 3. Evans' aldol reaction[17] of **19** with **20**[18] exclusively produced aldol **21**, which was converted to **4** through protection with TBSOTf and hydrolysis of the ester part. Thus, the C1–C7 part **4** was simply prepared in only three steps in 92% overall yield from **20**. Finally, the condensation reaction of **4** with **3** using DCC and DMAP (82%) followed by detachment of PMB and Swern oxidation (overall 52%) successfully produced the left-half part **2**.[19]

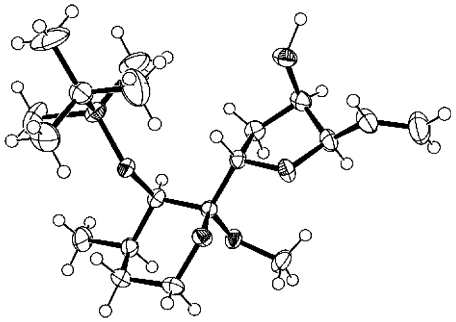
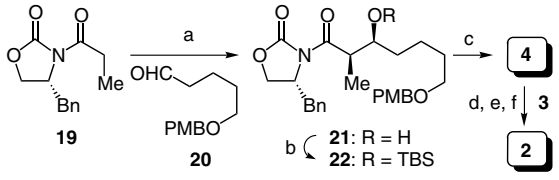


Figure 1. ORTEP diagram of **3**: one of the two crystallographically independent molecules is shown.



Scheme 3. Reagents and conditions: (a) Bu_2BOTf, Et_3N, CH_2Cl_2, 0 °C, 1 h, then **19** (0.5 equiv), −78 → 0 °C, 4 h, ~100% from **19**; (b) TBSOTf, 2,6-lutidine, 0 °C, 1 h, 98%; (c) LiOH, 30% H_2O_2 aq, THF–H_2O, 24 °C, 4 h, 94%; (d) **3** (0.25 equiv), DCC, DMAP, CH_2Cl_2, 23 °C, 2 h, 82% from **3**; (e) DDQ, CH_2Cl_2–H_2O (10:1), 0 °C, 50 min, 82%; (f) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 10 min, then Et_3N, −78 → 0 °C, 20 min, 52%.

In conclusion, the common left-half [C31–C33(OC1–C7)–C40] part (**2**) of PTXs has been synthesized convergently from the C31–C35, C36–C40, and C1–C7 parts (**6**, **5**, and **4**, respectively). Connection of **6**, prepared via a new route shorter than our previous route, with **5** through reductive lithiation and addition reactions gave adduct **14** stereoselectively, which was converted to the C31–C40 part **3**. The left-half was synthesized by a three-step process including esterification of **3** with **4**. Further studies toward the total synthesis of PTXs are currently underway in this laboratory.

Crystallographic data (excluding structure factors) of **3** have been deposited with the Cambridge Crystallographic Data Center as supplementary publication numbers CCDC 269076. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

Acknowledgements

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16. Crystal data of **3**: $C_{19}H_{36}O_5Si$, M 372.58, orthorhombic $P2_12_12$ (No. 18), $a = 18.181(4)$ Å, $b = 22.563(5)$ Å, $c = 10.657(2)$ Å, $U = 4371(1)$ Å^3 D_c $(Z = 8) = 1.132$ g/cm^3, $T = 153$ K, $\mu = 1.30$ cm^{-1}. The final R value is 0.030 for 4944 independent reflections with $I > 3\sigma I$ and 452 parameters.
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19. Selected spectral data of **2**: $[\alpha]_D^{23}$ −31 (*c* 0.195, $CHCl_3$); ^{1}H NMR (300 MHz, C_6D_6) δ 0.02 (3H, s), 0.09 (3H, s), 0.11 (3H, s), 0.13 (3H, s), 0.82–0.92 (1H, m), 0.83 (3H, d, $J = 7.2$ Hz), 0.99 (9H, s), 1.00 (9H, s), 1.27 (3H, d, $J = 7.2$ Hz), 1.35–1.55 (6H, m), 1.73–1.91 (3H, m), 2.05–2.25 (3H, m), 2.58 (1H, dq, $J = 5.1$, 7.2 Hz), 3.28 (1H, d, $J = 1.5$ Hz), 3.45 (3H, s), 3.48 (1H, ddd, $J = 2.9$, 11.2, 13.0 Hz), 3.74 (1H, br dd, $J = 4.4$, 11.2 Hz), 4.10 (1H, br q, $J = 5.1$ Hz), 4.41 (1H, tdd, $J = 1.5$, 4.2, 5.7 Hz), 4.87 (1H, dd, $J = 7.0$, 9.5 Hz), 5.16 (1H, td, $J = 1.5$, 10.5 Hz) 5.41–5.47 (1H, m), 5.46 (1H, td, $J = 1.5$, 17.3 Hz), 6.01 (1H, ddd, $J = 5.7$, 10.5, 17.3 Hz), 9.29 (1H, t, $J = 1.5$ Hz); ^{13}C NMR (75 MHz, C_6D_6, $^{13}C^{12}C_5D_6$ as 128.0 ppm) δ −4.3 (CH_3), −4.1 (CH_3), −3.4 (CH_3), −2.6 (CH_3), 11.8 (CH_3), 17.8 (C), 18.3 (CH_2), 19.0 (C), 19.1 (CH_3), 26.1 (CH_3), 26.7 (CH_3), 27.2 (CH_2), 30.1 (CH), 33.7 (CH_2), 35.1 (CH_2), 43.6 (CH_2), 45.0 (CH), 50.1 (CH_3), 62.3 (CH_2), 73.29 (CH), 73.34 (CH), 76.1 (CH), 81.1 (CH), 81.8 (CH), 99.2 (C), 117.2 (CH_2), 134.5 (CH), 173.9 (C), 200.1 (CH); IR (film) ν_{max} 3082, 2952, 2929, 2884, 2857, 2712, 1729, 1658, 1473, 1463, 1389, 1361, 1253, 1220, 1172, 1127, 1099, 1054, 1006, 995, 931, 837, 809, 776, 666 cm^{-1}; LR-FDMS, *m/z* 643 (7%, $[M+H]^+$), 610 (19%, $[M-MeOH]^+$), 585 (bp, $[M-{}^tBu]^+$); HR-FDMS, calcd for $C_{33}H_{63}O_8Si_2$ $[M+H]^+$: 643.4062, found: 643.4087.