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Improved synthesis of C8–C20 segment of pectenotoxin-2

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ABSTRACT

The C8–C20 segment of pectenotoxin-2 was efficiently synthesized in 16% overall yield in 22 steps from L-malic acid via an improved route.

Pectenotoxin-2 (**1**, Fig. 1) was first isolated from Japanese scallop *Patinopecten yessoensis* and the dinoflagellate *Dinophysis fortii* and characterized as a causative toxin of diarrhetic shellfish poisoning by Yasumoto.[1] Further, pectenotoxin-2 possesses a specific 34-membered macrolactone framework with a non-anomeric [6,5]-spirocyclic acetal (AB-ring),[2] a bicyclic acetal (D-ring), three oxolanes (C-, E-, and F-rings), and a six-membered cyclic hemiacetal (G-ring).[1] The macrolide also exhibits strong cytotoxicity against cancer cells due to actin-depolymerization.[3,4] Its unusual structural and biological properties have prompted us to initiate a program directed toward the total synthesis of **1**.[5]

Since the absolute stereochemistry of pectenotoxin-6, a congener with a carboxy group instead of the methyl group at C18 of **1**, was determined in 1997,[1b] several research groups have reported their extensive efforts toward achieving the total synthesis of the pectenotoxin family of natural compounds.[6] In 2002, the Evans group achieved the first total synthesis of pectenotoxins-4 and -8, which are the C18-hydroxymethyl-congeners of **1** having an anomeric-[6,5]-spirocyclic acetal or a [6,6]-spirocyclic acetal, respectively, as the AB-ring.[7,8]

During the course of our program, we achieved the synthesis of the left half of **1** (**2**),[5c] C21–C30 segment **3**,[5d] and C8–C20 segment **4**[5d] (Scheme 1). However, the output of **4** (0.3% overall yield in 31 steps from L-malic acid) was insufficient for further investigations, and therefore, the synthetic route was reconsidered. In this study, we describe an efficient synthesis of a new C8–C20 segment of **1** (**5**; 16% overall yield in 22 steps from L-malic acid).

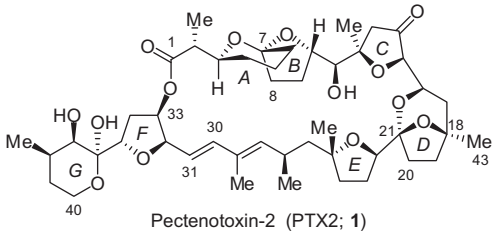
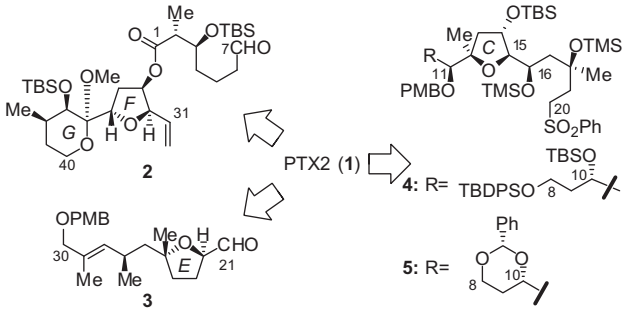


Figure 1.



Scheme 1.

The retrosynthesis of C8–C20 segment **5** is outlined in Scheme 2. Phenyl sulfone **5**, of which the benzylidene acetal was used for the protection of the oxygen atoms at C8 and C10, was newly designed for the C8–C20 segment. For obtaining high efficiency in the synthesis of **5**, we employed a convergent synthetic route and reduced the

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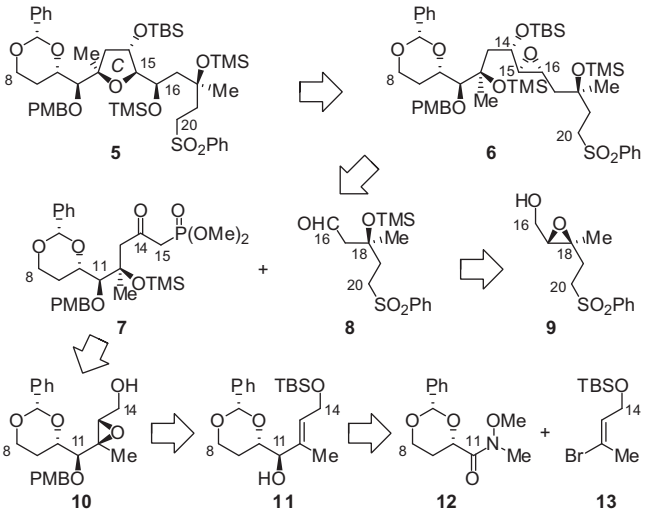
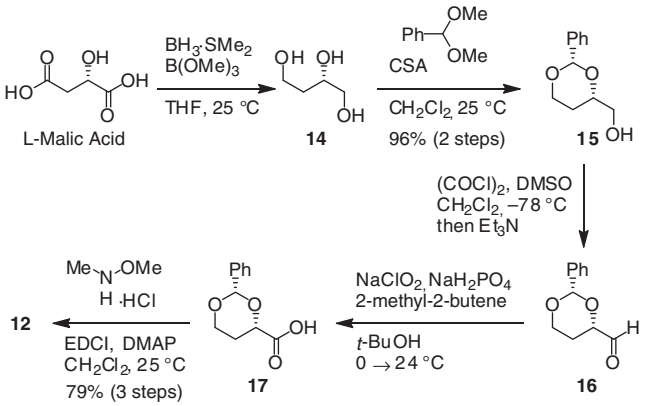


Scheme 2.

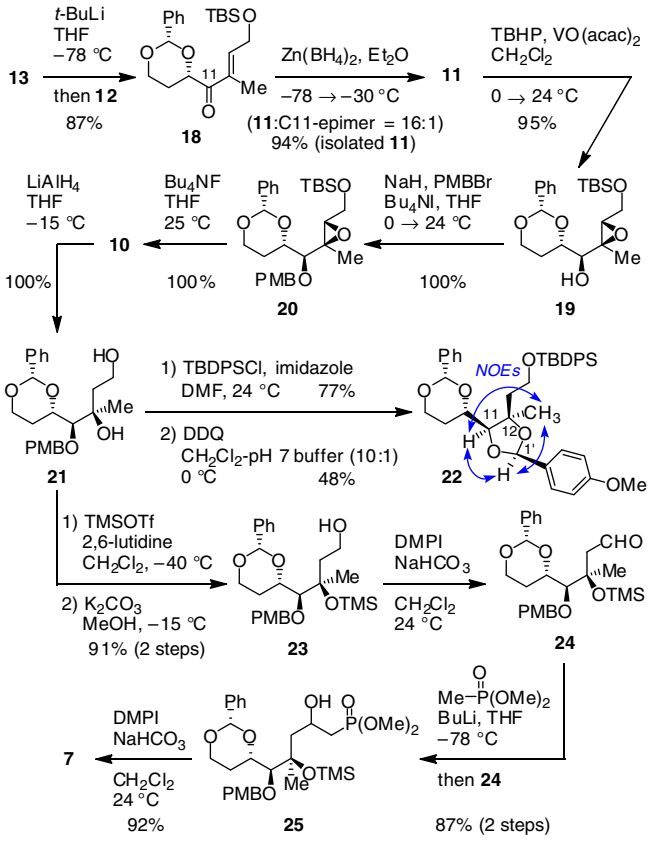
number of protection/deprotection steps. The benzylidene acetal and the phenyl sulfonyl groups of **5** were used in its original form from the starting materials **12** and **9**, respectively. The assembly of **5** from C8–C15 segment **7** and C16–C20 segment **8** was undertaken according to our previous synthesis:[5d] the C-ring would be constructed by the 5-*exo* cyclization of epoxide **6**, which would be formed through the Horner–Wadsworth–Emmons reaction between **7** and **8**, stereoselective reduction of the ketone at C14, and diastereoselective epoxidation at C15–C16. For the synthesis of phosphonate **7**, we planned a simple route starting from **12** and **13**,[9] which relied on a process including the construction of **11** by a coupling reaction of **12** with an anion from **13** followed by stereoselective reduction, selective formation of **10** via stereocontrolled epoxidation at C12–C13 of **11**, and the installation of a phosphonate group. Aldehyde **8** would be prepared from epoxide **9** via regioselective reductive cleavage followed by oxidation.

Amide **12** was synthesized from L-malic acid, which was first converted to **15** by reduction with borane followed by acetalization with benzaldehyde dimethyl acetal (96% over two steps) (Scheme 3).[10] Further, **15** was subjected to a three-step process involving Swern oxidation,[11] Pinnick oxidation,[12] and condensation with *N*,*O*-dimethylhydroxylamine to produce **12** (79% yield over three steps).

The synthesis of phosphonate **7** from amide **12** and bromoalkene **13**[9] is illustrated in Scheme 4. After **13** was lithiated with *t*-BuLi, the resulting alkenyllithium was reacted with **12** to afford enone **18** (87%),[13] which was diastereoselectively reduced with



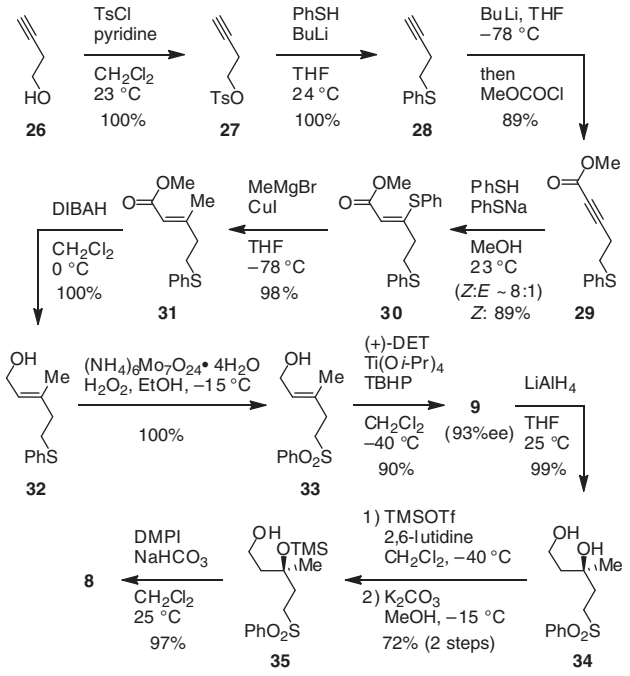
Scheme 3.



Scheme 4.

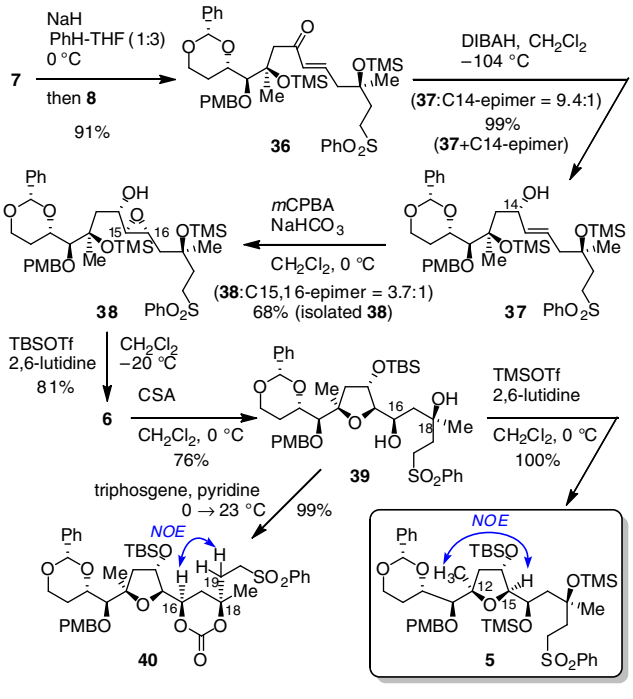
$Zn(BH_4)_2$ to produce **11** (94%) and a small amount of its C11-epimer (6%).[14] The absolute configuration at C11 of **11** was determined by modified Mosher's method.[15] Further, the epoxidation of **11** under Oshima's conditions[16] led to **19** as a single diastereomer in 95% yield. The hydroxy group of **19** was protected with 4-methoxybenzyl bromide (PMBBr) (100%), and the resulting **20** was desilylated with Bu_4NF to give **10** (100%). When **10** was treated with $LiAlH_4$ at −15 °C, the epoxide was regioselectively cleaved, and diol **21** was produced quantitatively. In order to confirm the stereochemistry at C12, diol **21** was first converted to acetal **22** by sequential protection with *tert*-butyldiphenylsilyl chloride (TBDPSCl) (77%) and oxidative acetalization (48%).[17] Acetal **22** was then analyzed by NMR spectroscopy, and the observed NOE correlations among H11, H1', and CH_3 at C11 indicated that these protons were located at the same side of the 1,3-dioxolane ring of **22**; this clearly establishes the *R*-configuration at C12 based on the *S*-configuration at C11. Diol **21** was subsequently transformed to trimethylsilyl (TMS) ether **23** through a full-protection/partial-deprotection process (91% over two steps). Dess–Martin oxidation[18] of **23** followed by a reaction with an anion of dimethyl methylphosphonate produced alcohol **25** (87% over two steps), which was oxidized to furnish phosphonate **7** (92%).

The synthesis of C16–C20 segment **8** was started from 3-butyn-1-ol (**26**) (Scheme 5). The tosylation of **26** (100%) followed by the substitution with lithium thiophenolate produced **28** (100%), which was then reacted with methyl chloroformate under basic conditions to give **29** (89%). The stereoselective conversion of **29** into **31** was conducted according to the Kobayashi–Mukaiyama procedure:[19] *Z*-selective addition of thiophenol to **29** afforded **30** (89%), which was then reacted with MeMgBr in the presence of CuI to yield **31** with retention of stereochemistry (98%). Ester **31** was reduced to **32** with diisobutylaluminum hydride (DIBAH) (100%). Because the direct transformation of **32** into **9** under



Scheme 5.

Katsuki–Sharpless asymmetric epoxidation conditions[20] resulted in a low yield due to the sluggish oxidation of the phenylthio group, a two-step oxidation/epoxidation was applied to **32**. The oxidation of **32** with H_2O_2 in the presence of $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ selectively produced **33** (100%),[21] and **33** was subjected to Katsuki–Sharpless asymmetric epoxidation[20] using (+)-diethyl tartrate (DET) to furnish **9** successfully (90%, 93%ee).[22] The epoxide of **9** was regioselectively cleaved with $LiAlH_4$ (99%), and the resulting diol **34** was converted to TMS ether **35** via a stepwise protection/deprotection process (77% over two steps). Finally, the Dess–Martin oxidation[18] of **35** produced aldehyde **8** corresponding to the C16–C20 segment of **1** (97%).



Scheme 6.

The assembly of **5** was started from the Horner–Wadsworth–Emmons reaction between **7** and **8**, which selectively yielded **36** (91%) (Scheme 6). The reduction of **36** with DIBAH below −100 °C stereoselectively produced **37** as an inseparable mixture with its C14-epimer (99% yield, **37**:C14-epimer = 9.4:1). After intensively investigating the optimum conditions for the stereoselective epoxidation of the olefin at C15–C16 of **37** or its derivatives, we found that the epoxidation of **37** with *m*CPBA in the presence of $NaHCO_3$ in CH_2Cl_2 at 0 °C gave relatively good results—epoxide **38** was furnished as a major component in 68% isolated yield (the NMR ratio of **38** to its C15,16-epimer in the crude mixture was 3.7:1). Alcohol **38** was protected with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) to afford **6** (81%). The treatment of **6** with 10-camphorsulfonic acid (CSA) promoted the removal of the TMS groups and the simultaneous 5-*exo* cyclization to produce **39** (76%), which was then transformed to **5**[23] with TMSOTf (100%).

The configuration at C15 of **5** was proved to be *R* by the presence of an NOE enhancement between H15 and the CH_3 group at 12*R*-stereocenter. The determination of the *R*-configuration at C16 relied on the application of modified Mosher's method to **39**.[15] Further, the *R*-configuration at C18 was confirmed by the presence of the NOE correlation between H19 and the proton at 16*R*-stereocenter of cyclic carbonate **40**, derived from **39**.

In conclusion, the C8–C20 segment (**5**) of pectenotoxin-2 (**1**) was efficiently synthesized in 16% overall yield in 22 steps from L-malic acid via an improved route. Further efforts toward the total synthesis of PTX2 are currently underway in our laboratory.

Acknowledgments

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22. The enantiomeric purity of **9** was determined by HPLC analysis using a chiral column (CHIRALPAK IA, Daicel Chemical Industries, 4.6 mm × 25 cm, hexane/EtOH = 2:1, flow rate = 1 ml/min).
23. Selected spectral data of **5**: a colourless oil; $[\alpha]_D^{24}$ +32.0 (*c* 0.165, $CHCl_3$); ^1H NMR (C_6D_6, 400 MHz, 7.15 ppm for C_6HD_5) δ 0.002 (6H, s) 0.08 (9H, s), 0.24 (9H, s), 0.92 (9H, s), 1.18 (3H, s), 1.31 (1H, br d, *J* = 13.5 Hz), 1.44 (3H, s), 1.70–1.82 (3H, m), 2.06–2.15 (3H, m), 2.28 (1H, br dq, *J* = 4.8, 12.6 Hz), 3.25–3.40 (2H, m), 3.31 (3H, s), 3.58 (1H, br ddd, *J* = 2.3, 11.3, 12.6 Hz), 3.66 (1H, br s), 4.02 (1H, br dd, *J* = 4.8, 11.3 Hz), 4.09 (1H, dd, *J* = 1.8, 5.6 Hz), 4.14–4.19 (1H, m), 4.22–4.29 (1H, m), 4.36 (1H, br d, *J* = 10.9 Hz), 4.69 (1H, d, *J* = 11.5 Hz), 4.86 (1H, d, *J* = 11.5 Hz), 5.49 (1H, s), 6.79 (2H, d, *J* = 8.7 Hz), 6.88–6.98 (3H, m), 7.11–7.16 (1H, m), 7.23–7.30 (4H, m), 7.75 (2H, br d, *J* = 7.8 Hz), 7.85–7.89 (2H, m); ^{13}C NMR (C_6D_6, 100 MHz, 128.0 ppm for C_6D_6) δ −4.7 (CH_3), −4.2 (CH_3), 1.1 ($CH_3 \times 3$), 2.6 ($CH_3 \times 3$), 17.9 (C), 22.5 (CH_3), 25.9 ($CH_3 \times 3$), 27.4 (CH_2), 27.9 (CH_3), 36.3 (CH_2), 44.6 (CH_2), 47.4 (CH_2), 52.7 (CH_2), 54.7 (CH_3), 66.6 (CH_2), 69.7 (CH), 72.3 (CH), 73.4 (CH_2), 74.8 (C), 78.6 (CH), 83.5 (C), 85.9 (CH), 88.8 (CH), 102.0 (CH), 114.0 (CH × 2), 126.6 (CH × 2), 128.3 (CH × 4), 128.7 (CH), 129.2 (CH × 2), 130.4 (CH × 2), 130.8 (C), 133.0 (CH), 140.1 (C), 140.8 (C), 159.8 (C); IR (film) ν_{max} 3066, 3035, 2955, 2896, 2857, 1612, 1586, 1514, 1463, 1447, 1369, 1305, 1249, 1211, 1173, 1098, 1038, 938, 838, 776, 751, 697, 689, 650 cm^{-1}; HR-FDMS calcd for $C_{48}H_{76}O_{10}Si_3S$ [M^+]: 928.4467, found: 928.4467.