5′-amino and 3′-acetaldehyde groups remain at the end of the reaction.

As in the polymerase chain reaction (PCR),[20–22] $S(dAp)_8$ templates the ligation of multiple monomers in a single reaction cycle. Unlike PCR, where both strands of the DNA duplex are amplified to give exponential growth, the DNA-templated polymerization reactions employ only a single strand as the template and growth is presumably linear with each reaction cycle. In addition, the requirement for primers compatible with the double-strand-binding polymerase is avoided, and short sequences of DNA are amplified efficiently.

Finally, the reaction does not synthesize native DNA, but a backbone analogue. Therefore, solid-supported oligomeric DNA can be used to catalyze the rapid synthesis of polymers containing different backbones simply by changing the structure of the reactant, in this case $(T)_1$ and $(T_N)_2$, Quite unlike other solid-supported syntheses, $S(dAp)_n$ can be used repeatedly both to catalyze the polymerization as well as purify the product, which greatly reduces the time and effort for the synthesis of modified DNA-analogues. The extension of this chemistry to mixed-sequence templates should enable the rapid amplification of DNA sequence information into specific backbone-modified analogues. Moreover, this general strategy for solid-phase synthesis can now be extended more broadly, through other molecular recognition elements, to accomplish chain-length-specific polymerizations.

Experimental Section

DNA Synthesis: All native DNA oligomers were prepared by the Emory University Microchemical Facility on a PE-Biosystems 394 DNA Synthesizer. The DNA $S(dAp)_8$ template was synthesized on OAS-PS (Glen Research, Batch No. G008062, Cat. No. 26-4001) solid supports by standard cyanoethyl phosphoramidite chemistry. The linker of OAS-PS is stable to the last step of ammonium hydroxide deprotection treatment in the automated synthesis. To confirm purity, the DNA oligomers were removed from the resin and analyzed by Rainin HPXL RP-HPLC: Phenomenex Prodigy 5 analytical ODS(2) C18; Rainin Dynamax UV detector at 260 nm, and eluted with MeOH in H_2O (0–100 % in 50 min), and the structure confirmed by MALDI-MS: $C_{80}H_{97}N_{40}O_{38}P_7$ calcd m/z: 2443.69 $[M{+}H^+]$; found 2444.87.

Polymerization: The substrates, 8 mM for $(T_N)_2$ and 16 mM for $(T)_1$, were mixed with $S(dAp)_8$ at the indicated stoichiometry, heated to 75 °C for 2–3 min, and cooled to 4 °C for 3 h.[23] $NaBH_3CN$ (20 equiv) was added at room temperature and the mixture stirred vigorously in a vortex mixer for 72 h, with the addition of more $NaBH_3CN$ (10 equiv) after 48 h to ensure complete reaction. The mixture was subjected to centrifugation in the Ultrafree-MC (Millipore Corp.) centrifugal filter tube at room temperature to remove the reagents, and the beads resuspended in MeOH, heated to 75 °C, and subjected to centrifugation whilst hot, with 3 × 1 mL MeOH. The MeOH washes were combined, evaporated to dryness, and analyzed by reverse-phase HPLC (same system as above), and eluted with MeOH in H_2O: 0–5 % from 0–8 min, 5–20 % from 8–9 min, 20–35 % from 9–24 min, 35–60 % from 24–25 min, 60–100 % from 25–50 min. The product assignments were justified by co-injection with standard samples and by mass spectrometry. MALDI-TOF (2′,4′,6′-trihydroxyacetophenone monohydrate (THAP)/citrate): $(T_N)_2$-[NH-$(T_N)_2]_3$-CHO, $C_{96}H_{128}N_{24}O_{29}$ calcd m/z: 2080.9279 $[M^+]$; found 2082.85 $[M{+}2H]^+$; $(T_N)_2$-[NH-$(T_N)_2]_3$-CH_2OH, $C_{96}H_{130}N_{24}O_{29}$ calcd m/z: 2082.9436 $[M^+]$; found 2083.84 $[M{+}H]^+$; $(T)_1$-[NH-$(T)_1]_7$, $C_{96}H_{136}N_{24}O_{25}$, calcd m/z: 2025.0109 $[M^+]$; found 2026.12 $[M+H]^+$.

For resin recovery, the beads were washed 3 × 1 mL with deionized H_2O and resuspended in H_2O overnight under vortex mixing before being used for the next reaction cycle.

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Asymmetric Syntheses of Pectenotoxins-4 and -8, Part I: Synthesis of the C1–C19 Subunit[**]

David A. Evans,[*] Hemaka A. Rajapakse, and
Dirk Stenkamp

The first members of the pectenotoxin family of marine natural products were isolated off the northeastern coast of Japan in 1985. Subsequently, ten members of this group have been identified.[1] The structural diversity within the pectenotoxins stems from variations in the oxidation state at C43, as well as the differing configurations of the AB spiroketal portion of the structures. Pectenotoxin-2 (C43 = Me) is cytotoxic towards human lung, colon, and breast cancer cell lines with LC_{50} values in the nanomolar range.[1c] Pectenotox-

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ins-1, -4, and -8 (C43 = CH$_2$OH) are differentiated by their AB spiroketal subunits that are interconvertable by acid equilibration (Figure 1, Eq. (1)).[1b] While no total synthesis of any pectenotoxin has been reported, there have been efforts directed toward the synthesis of these architecturally complex natural products.[2] In this and the following communication,[3] we describe our efforts culminating in the synthesis of pectenotoxin-4 (**1**).

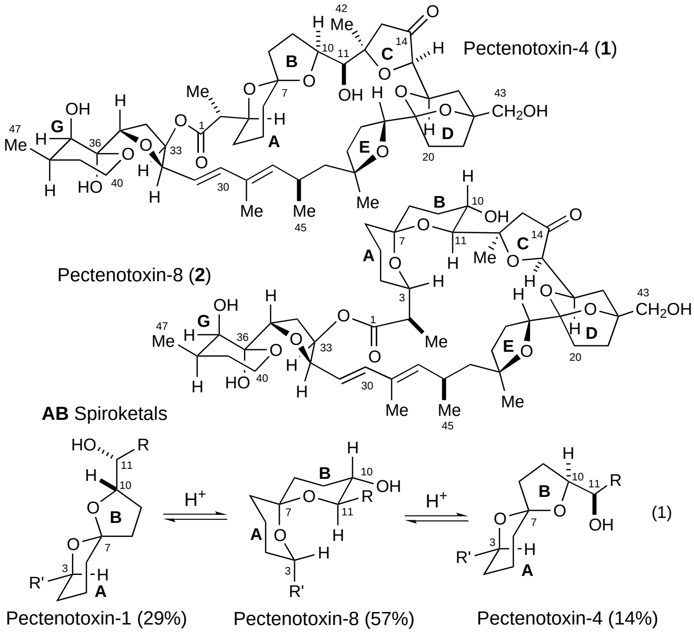
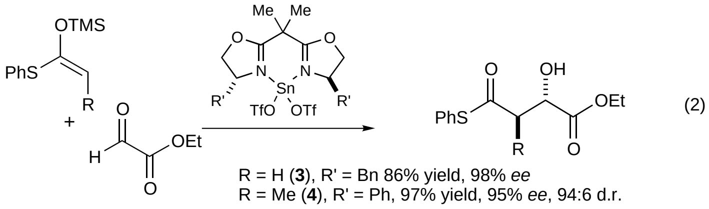


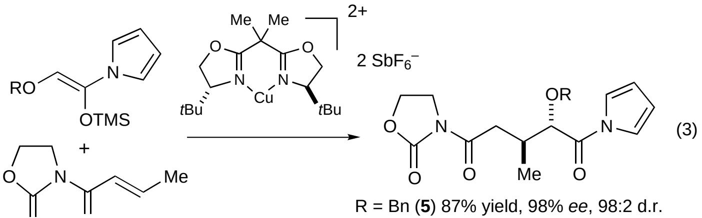
Figure 1. The pectenotoxin family of natural products, and their interconversion by acid equilibration [Eq. (1)].

Pectenotoxin-4 was chosen as our initial target. Although this spiroketal is the most stable isomer in acyclic precursors it becomes the least favored when constrained in the macrolide framework.[1b,d] Our principal disconnections are illustrated in Scheme 1. Application of the macrolactonization transform and ring opening of the D-ring bicyclic ketal reveals intermediate **I**, a synthesis subgoal that might be assembled from fragments **II** and **III** through a metalloenamine-epoxide alkylation.[4] The synthesis plan calls for masking the ketones at C14 and C36 as protected alcohols until late in the synthesis. Protection of the carboxylate terminus at C1 as its derived *N*-phenylamide would enable the preservation of the C1 carboxyl carbon atom in its correct oxidation state throughout the synthesis.[5] In the retrosynthesis of the ABC tricyclic fragment **II**, convenient disconnections could be made about the C16–C17 and C11–C12 bonds (Scheme 1). The stereocenters at C11 and C16 could be constructed by chelate-controlled reduction of the corresponding ketone, or by Felkin-controlled addition of an appropriate nucleophile to the respective aldehydes.

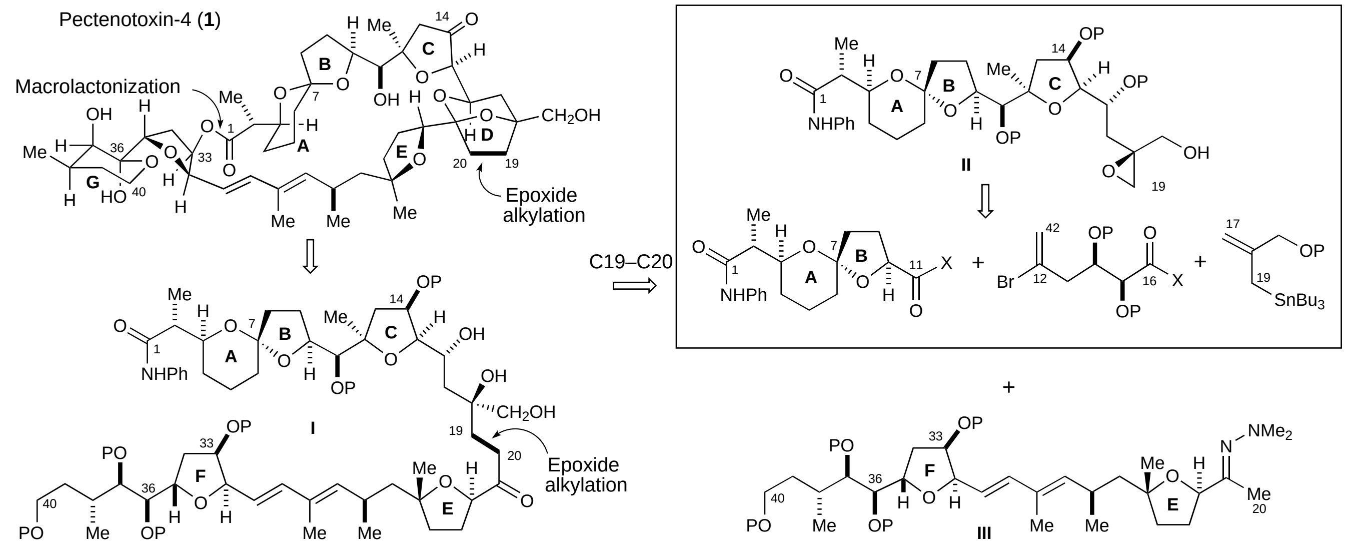
The integration of catalytic enantioselective processes into our synthesis projects has been an ongoing objective. In this regard, the enantioselective Sn^{2+}-catalyzed aldol reaction [Eq. (2)] provides the foundation for the synthesis of the C8–C11 acetate and C36–C39 propionate fragments.[6,7] The asymmetric Michael addition reaction reported from these laboratories provides a useful alternate route for the construction of the C36–C40 propionate fragment [Eq. (3)].[8]



R = H (**3**), R' = Bn 86% yield, 98% *ee*
R = Me (**4**), R' = Ph, 97% yield, 95% *ee*, 94:6 d.r.

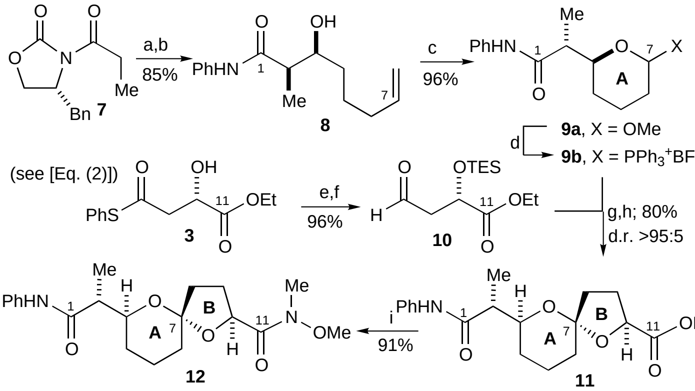


R = Bn (**5**) 87% yield, 98% *ee*, 98:2 d.r.
R = TBS (**6**), 75% yield, 95% *ee*, 98:2 d.r.



Scheme 1. Retrosynthetic analysis of pectenotoxin-4.

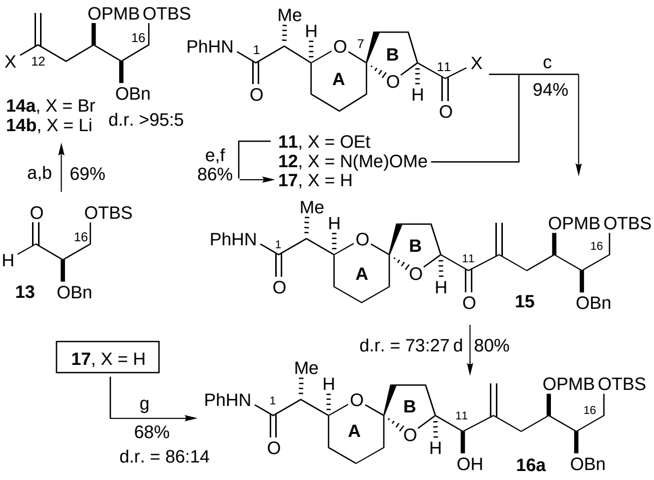
Synthesis of the AB spiroketal began with the addition of the boron enolate derived from **7** to 5-hexenal, which afforded the desired *syn*-aldol adduct in 87% yield (d.r. > 95:5; Scheme 2).[9] Transamidation to *N*-phenylamide **8** (AlMe_3, aniline, CH_2Cl_2, 98%), olefin ozonolysis, followed by in situ ether formation afforded the A-ring lactol methyl ether **9a**. In preparation for a Wittig-based fragment coupling, **9a** was transformed into the anomeric phosphonium salt **9b** ($\text{PPh}_3\cdot\text{HBF}_4$, CH_3CN, 60°C).[10] The aldehyde partner **10** was readily accessed by protection of aldol adduct **3**, followed by chemoselective half reduction of the *S*-phenyl thioester under conditions (Pd/C, Et_3SiH, acetone, 97%) reported by Fukuyama et al.[11]



Scheme 2. Synthesis of the AB spiroketal. a) 1. $n\text{Bu}_2\text{BOTf}$, Et_3N, CH_2Cl_2, −78°C; 2. 5-hexenal, CH_2Cl_2, −78°C; 87%; b) AlMe_3, aniline; CH_2Cl_2; 98%; c) 1. O_3, MeOH, then DMS, −78°C; 2. CSA; 96%; d) $\text{PPh}_3\cdot\text{HBF}_4$, CH_3CN, 60°C; e) TESOTf, lut., CH_2Cl_2, −78°C; 99%; f) Pd/C, Et_3SiH, acetone; 97%; g) 1. 2 equiv $n\text{BuLi}$, THF, −78°C; 2. aldehyde **10**; h) CSA, $\text{MeOH/CH}_2\text{Cl}_2$ (1:1); 80% (three steps); i) MeONHMe·HCl, $i\text{PrMgCl}$,THF, −78°C→−20°C; 91%. See reference [7] for abbreviations.

Wittig coupling of the ylide derived from **9b** and aldehyde **10** afforded the corresponding enol ether, which was immediately subjected to camphorsulfonic acid (CSA) in MeOH to provide the desired AB spiroketal **11** in 80% overall yield (d.r. > 95:5). In preparation for the next fragment coupling, the ethyl ester group at C11 of **11** was transformed to the Weinreb amide **12** by using a modified literature procedure.[12]

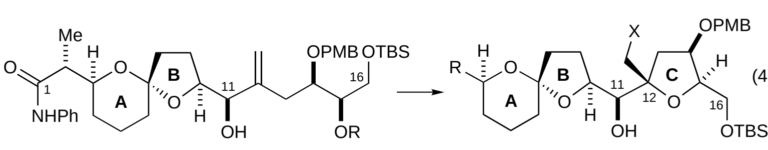
With the spiroketal in hand, the C11–C12 bond construction was examined. The desired C12–C16 *syn*-diol was readily accessed from the allylation of the differentially protected glyceraldehyde derivative **13** (d.r. > 95:5; Scheme 3).[13] PMB protection of the resulting C14 alcohol required the use of PMB-trichloroacetimidate.[14] Attempts to employ basic conditions resulted in the formation of alkyne by-products from the elimination of hydrogen bromide. Lithium–halogen exchange of vinyl bromide **14a** ($t\text{BuLi}$, Et_2O/pentane, −78°C), followed by addition of Weinreb amide **12** afforded the desired C1–C16 carbon chain. Reduction of the resulting carbonyl group at C11 in **15** afforded moderate chelate-controlled diastereoselectivity with $\text{Zn(BH}_4)_2$ (d.r. 73:27, 80% yield). The use of superior chelating reagents such as LiBHBu_3 afforded better selectivity[15] (d.r. 81:19, 58% yield), but resulted in competitive 1,4-reduction (38%).



Scheme 3. Synthesis of C1–C16 Fragment **16a**. a) $[\text{Ti}(\text{O}i\text{Pr})\text{Cl}_3]$, 2-bromoallyltrimethylsilane, CH_2Cl_2, −78°C; 87%; b) PMB-trichloroacetimidate, TfOH, Et_2O, −20°C→0°C; 79%; c) **14a**, $t\text{BuLi}$, Et_2O/pentane, −78°C then **12**; 94%; d) $\text{Zn(BH}_4)_2$, $\text{Et}_2\text{O/CH}_2\text{Cl}_2$, −40°C; 80%; e) LiBH_4, THF, −10°C; 93%; f) $\text{SO}_3\cdot\text{Py}$, Et_3N, $\text{DMSO/CH}_2\text{Cl}_2$ (1:1); 91%; g) **14a**, $t\text{BuLi}$, Et_2O, −78°C, then MgBr_2, then aldehyde **17**, Et_2O, −78°C; 68%. See reference [7] for abbreviations.

A viable alternative to the construction of **16a** was to access the stereocenter at C11 *directly* by a Felkin-controlled addition to the corresponding spiroketal aldehyde **17**.[16] The desired aldehyde **17** was accessed in two steps:[17] full reduction of the ethyl ester (LiBH_4, THF, −10°C, 94%) followed by Parikh–Doering oxidation ($\text{SO}_3\cdot\text{Py}$, Et_3N, CH_2Cl_2/DMSO, −10°C, 91%).[18] The Grignard reagent derived from vinyl bromide **14** added to aldehyde **17** to afford **16a** with good selectivity (86:14) and yield (68%).[19]

The completion of the fragment synthesis began with an investigation into electrophile-induced heterocyclizations to form ring-C [Eq. (4)]. Unfortunately, all attempts to induce cyclization of either **16a** or **16b** with either halogenating agents or with mercuric salts afforded the undesired ring-C C12 diastereomer **19**.

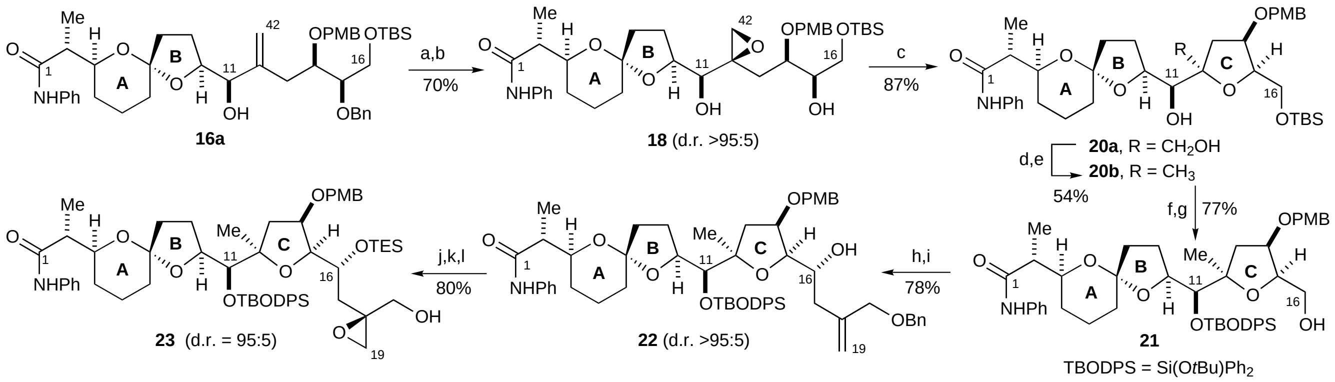


(4)

16a, R = Bn; **16b**, R = H

19, X = I, HgOAc; d.r. > 10:1

The successful solution to the ring-C construction and the synthesis of the ABC epoxide fragment began with the selective deprotection of the benzyl ether group at C15 under reducing conditions[20] (LiDBB, THF, −78°C, 81%) (Scheme 4). This step was followed by C11 hydroxy-directed epoxidation[21] ($[\text{VO(acac)}_2]$, TBHP, PhH, 99%, d.r. > 95:5) to afford a single epoxide diastereomer **18**, which was cyclized to **20a** under mildly acidic conditions (PPTS, CH_2Cl_2, 87%). Acylation of the primary alcohol with phenylthiono chloroformate (DMAP, CH_2Cl_2, −10°C, 75%), followed by



Scheme 4. Completion of C1–C19 ABC fragment. a) LiDBB, THF, −78 °C; 81 %; b) [VO(acac)$_2$], TBHP, PhH; 99 %; c) PPTS, CH_2Cl_2; 87 %; d) PhOC(S)Cl, DMAP, CH_2Cl_2, −10 °C; 75 %; e) Bu_3SnH, AIBN, xylenes, 160 °C; 72 %; f) TBODPSCl, DMAP, Et_3N, DMF; 90 %; g) CSA, CH_2Cl_2/MeOH (1:1), −20 °C; 85 %; h) SO_3·Py, Et_3N, CH_2Cl_2/DMSO (1:1), −10 °C; i) 2-(benzyloxymethyl) allyltributylstannane, BF_3·OEt_2, CH_2Cl_2, −78 °C; 78 % (two steps); j) TESCl, Im, CH_2Cl_2; 92 %; k) LiDBB, THF, −78 °C; 87 %; l) Ti(O*t*Bu)$_4$, (L)-(+)-DET, TBHP, 3 Å MS, CH_2Cl_2, −30 °C; 99 %. See reference [7] for abbreviations.

deoxygenation under standard Barton conditions completed the synthesis of the C-ring tetrahydrofuran **20b**.[22,23]

The hydroxy group at C11 was protected as a *tert*-butoxydiphenylsilyl (TBODPS) ether.[24] Selective deprotection of the primary TBS ether (CSA, CH_2Cl_2/MeOH), oxidation of the resulting alcohol **21** (SO_3·Py, Et_3N, CH_2Cl_2/DMSO, −10 °C)[18] to the unstable α,β-bisalkoxy aldehyde, followed by Felkin controlled allylation with 2-(benzyloxymethyl)allyltributylstannane[25] (BF_3·OEt_2, CH_2Cl_2, −78 °C, 78 % over two steps, d.r. 95:5) provided homoallyl alcohol **22**, the complete carbon chain of the C1–C19 fragment. Protection of the hydroxy group at C16 (TESCl, Im, CH_2Cl_2, 92 %), benzyl deprotection[20] (LiDBB, THF, −78 °C, 87 %), and a stoichiometric Sharpless asymmetric epoxidation[26] ([Ti(O*t*-Bu)$_4$], (L)-(+)-DET, TBHP, 3 Å MS, CH_2Cl_2, −30 °C, 99 %, d.r. 95:5) afforded the desired ABC epoxide **23** with excellent selectivity.

The preceding discussion describes the stereoselective synthesis of the C1–C19 ABC epoxide fragment of the pectenotoxin skeleton. The following communication describes the syntheses of the C20–C30 E-ring and C31–C40 FG fragments, and the fragment assemblage to pectenotoxin-4.

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[7] Abbreviations: OTf = trifluoromethanesulfonyl; Bn = benzyl, TBS = *tert*-butyldimethylsilyl; d.r. = diastereomeric ratio; TES = triethylsilyl; lut. = 2,6-lutidine; PMB = 4-methoxybenzyl; DMSO = dimethyl sulfoxide; LiDBB = lithium di-*tert*-butyl biphenylide; DMAP = 4-(*N*,*N*-dimethylamino)pyridine; AIBN = 2,2′-azobisisobutyronitrile; TBODPS = *tert*-butoxydiphenylsilyl; Im = imidazole; PPTS = pyridinium *para*-toluenesulfonate; DMF = dimethylformamide; CSA = camphorsulfonic acid; TBHP = *tert*-butyl hydroperoxide; DET = diethyl tartrate; MS = molecular sieves.

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Asymmetric Syntheses of Pectenotoxins-4 and -8, Part II: Synthesis of the C20–C30 and C31–C40 Subunits and Fragment Assembly**

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In the preceding communication,[1] the proposed synthesis plan identified the two principal pectenotoxin-4 subunits **II** and **III** (Figure 1). It was our intention to couple these fragments through the alkylation of the metalloenamine derived from hydrazone **III**, readily available from the coupling of advanced intermediates **IV** and **V** (transform T$_2$), by epoxide **II**. However, this investigation revealed that the above bond construction was not feasible due to the decomposition of metalloeneamine **III** under the reaction conditions.[2] Accordingly, the objective in the present communication is the synthesis of the subunits **IV** and **V**, and the completion of the syntheses of pectenotoxin-4 (**1**) and pectenotoxin-8 by a revised fragment coupling strategy, where epoxide alkylation (transform T$_1$) precedes diene formation (transform T$_2$).

The plan for the construction of the F-ring tetrahydrofuran **IV** was to involve a C37 hydroxy-directed epoxidation of olefin **VI** with a subsequent ring closure by the C32 hydroxy moiety (transform T$_3$). Finally, the stereoselective formation of the E-ring tetrahydrofuran **V** from its acyclic precursor **VII** was based on an iodoetherification precedent provided by Bartlett and Rychnovsky (transform T$_4$).[3]

The synthesis of the ring-E synthon **V** began with the known aldol adduct adduct **2** (Scheme 1).[4] Reduction of **2** (LiBH$_4$, THF, 0 °C), and selective protection of the primary alcohol (TBSCl, Im, CH_2Cl_2, 100 % over two steps) afforded allylic alcohol **3**.[5] Acylation of **3** with the PMB-protected lactic acid **4**[6] (DCC, DMAP, CH_2Cl_2, 52 %), followed by carbonyl olefination of **5a** with Tebbe reagent[7] afforded the 1,5-diene **5b**. Claisen rearrangement of **5b** in refluxing toluene gave the desired rearrangement product **6** in 82 % yield for the two steps. Chelate-controlled reduction of the resulting ketone ($Zn(BH_4)_2$, Et_2O, −78 °C, 86 %, d.r. 86:14) provided the precursor for the key iodoetherification reaction. In spite of the modest selectivity that was observed for the formation of the desired tetrahydrofuran **7** (NIS, CH_3CN, −40 °C, 89 %, d.r. 72:28), this outcome proved sufficient to pursue the planned route.

Successive radical dehalogenation of **7** (Bu_3SnH, AIBN, toluene, 100 %) and deprotection of the primary TBS ether (TBAF, THF, 95 %) afforded alcohol **8**. Oxidation with Dess–Martin reagent[8] (py, CH_2Cl_2, 99 %), Wittig homologation ($EtOC(O)CC(CH_3)PPh_3$, THF, 65 °C; 100 % E:Z > 95:5), and ester reduction ($LiAlH_4$, Et_2O, 0 °C, 92 %) completed the carbon assembly of the E-ring fragment. Benzyl protection (NaH, BnBr, TBAI, THF/DMF, 94 %) followed by PMB deprotection (DDQ, CH_2Cl_2/pH 7 buffer, 95 %) gave alcohol **10**. Oxidation to the methyl ketone[8] (Dess–Martin periodinane, py, CH_2Cl_2, 93 %), and hydrazone formation (TMSCl, CH_2Cl_2/Me_2NNH_2, 100 %) completed the synthesis of hydrazone **11**.

As summarized in Figure 1, the first stage of the synthesis of the ring-F fragment **IV** will be simplified to the construction of the C31–C35 phosphonium salt, the C36–C40 aldehyde, and their union through a Wittig coupling to afford the *Z*-olefin **VI**.

The synthesis of the C31–C35 phosphonium salt began with the known triol derivative **12** (Scheme 2).[9] Protection of the hydroxy group at C33 of **12** as a PMB ether (PMBBr, NaH, THF/DMF, 95 %) followed by reductive ozonolysis (O_3, EtOH, then DMS, then $NaBH_4$, 95 %) afforded alcohol **13**. Transformation of **13** to the corresponding iodide (I_2, Im, Ph_3P, CH_2Cl_2, 0 °C, 89 %) proceeded smoothly, but careful control of the temperature was required to access phosphonium salt **14** (Ph_3P, CH_3CN, 55 °C, 89 %).[10]

The synthesis of the aldehyde partner **17** began with protection of the hydroxy group at C37 of aldol adduct **15**[11] as a base-sensitive triphenylsilyl ether (TPSCl, Im, DMAP, DMF, 0 °C, 98 %; Scheme 2). Half reduction of the *S*-phenyl thioester[12] (Pd/C, Et_3SiH, acetone, 95 %), and olefination under modified Lombardo conditions[13] ([Cp_2ZrCl_2], Zn dust, CH_2I_2, THF, 0 °C, 84 %) afforded olefin **16**. Rhodium-

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