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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 metalloenamine **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

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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]

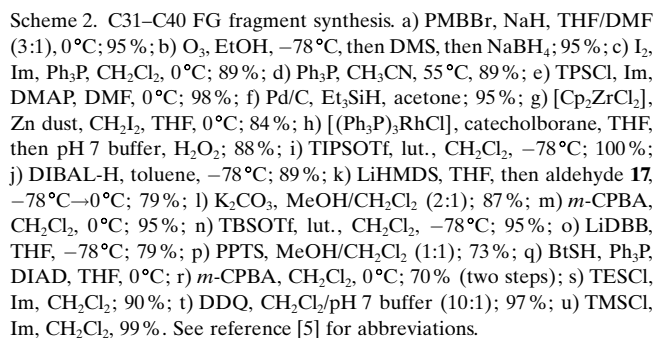
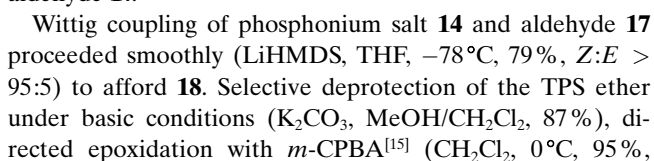
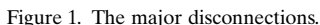
The synthesis of the ring-E synthon **V** began with the known aldol adduct adduct **2** (Scheme 1).^[4] Reduction of **2** (LiBH_4 , THF, 0 °C), and selective protection of the primary alcohol (TBSCl, Im, CH_2Cl_2 , 100 % over two steps) afforded allylic alcohol **3**.^[5] Acylation of **3** with the 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 ($\text{Zn}(\text{BH}_4)_2$, 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 ($\text{EtOC}(\text{O})\text{CC}(\text{CH}_3)\text{PPh}_3$, 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, $\text{CH}_2\text{Cl}_2/\text{pH 7 buffer}$, 95 %) gave alcohol **10**. Oxidation to the methyl ketone^[8] (Dess–Martin periodinane, py, CH_2Cl_2 , 93 %), and hydrazone formation (TMSCl , $\text{CH}_2\text{Cl}_2/\text{Me}_2\text{NNH}_2$, 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]

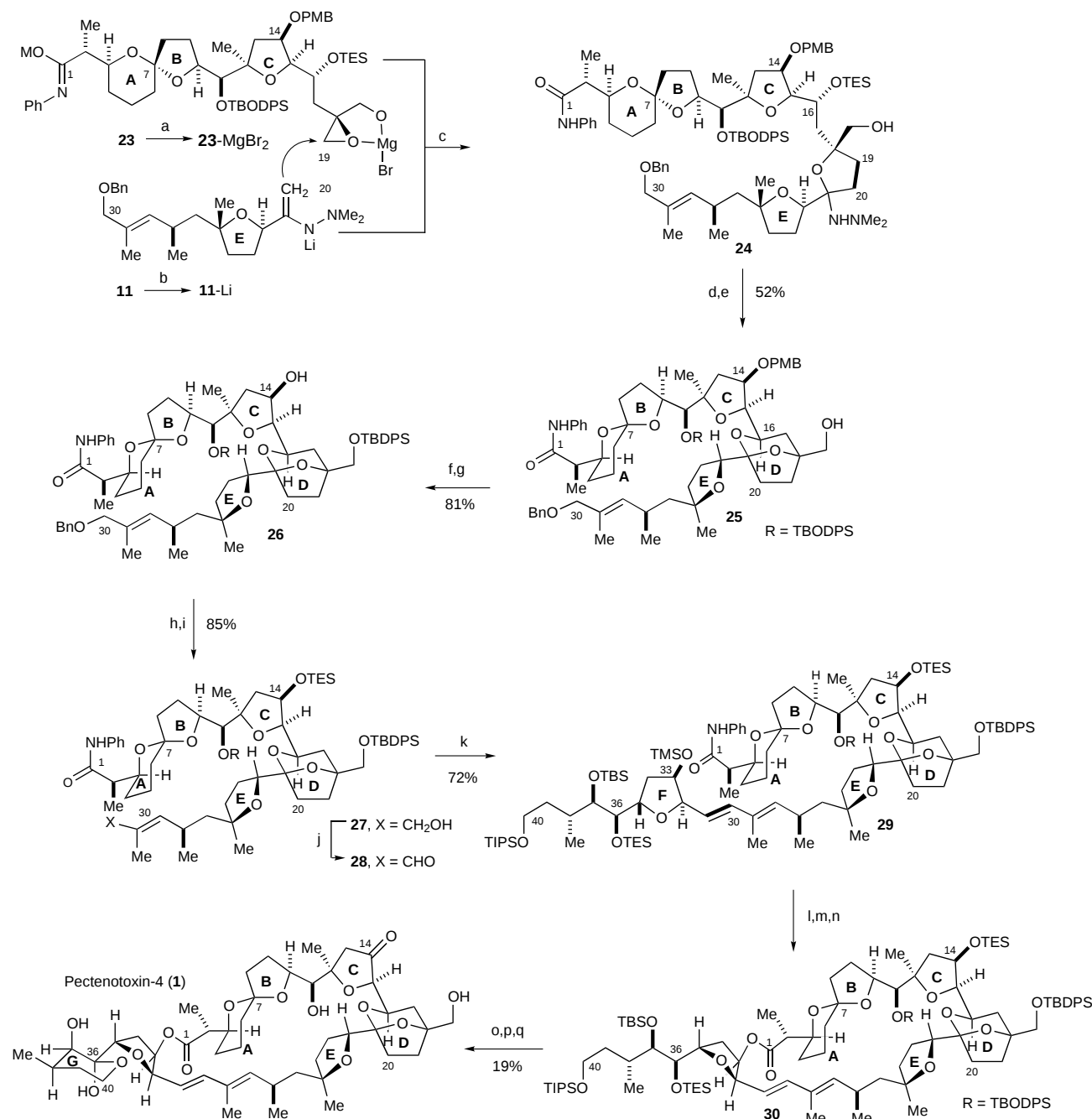
The synthesis of the aldehyde partner **17** began with protection of the hydroxy group at C37 of aldol adduct **15**^[11] as a base-sensitive triphenylsilyl ether (TPSCl, Im, DMAP, DMF, 0 °C, 98 %; Scheme 2). Half reduction of the S-phenyl thioester^[12] (Pd/C , Et_3SiH , acetone, 95 %), and olefination under modified Lombardo conditions^[13] ($[\text{Cp}_2\text{ZrCl}_2]$, Zn dust, CH_2I_2 , THF, 0 °C, 84 %) afforded olefin **16**. Rhodium-



(*m*-CPBA, CH₂Cl₂, 0 °C, 70 % over two steps), and protection of the hydroxy group at C36 as a TES ether (TESCl, Im, CH₂Cl₂, 90 %) afforded **21**. In preparation for the diene formation step, the C33-OPMB ether of sulfone **21** was exchanged for the corresponding TMS ether (DDQ, CH₂Cl₂/pH 7 buffer, 97 %; then TMSCl, Im, CH₂Cl₂, 0 °C, 99 %) to afford **22**.^[19]

Completion of the synthesis is shown in Scheme 3. The C19–C20 bond construction joining advanced intermediates

11 and **23** was accomplished by the addition of the magnesium bromide activated epoxide complex **23**-MgBr₂^[20] to the metalloenamine derived from **11**. The resulting unstable hydrazinyl lactol **24** was treated with acid under biphasic conditions (pentane/CH₂Cl₂/10 % aq. NaHSO₄) to access the corresponding lactol, which underwent desilylation at C16 and spontaneous bicyclic ketal formation to afford adduct **25** upon exposure to PPTS in MeOH/CH₂Cl₂ (52 % over three steps). Protection of the hydroxymethyl moiety at C18



Scheme 3. Fragment assembly and completion of synthesis. a) **23**, EtMgBr, HMPA, THF, −67 °C→0 °C; b) **11**, LDA, THF, −67 °C→0 °C; c) add **23**-MgBr₂ to **11**-Li, +10 °C; d) pentane/CH₂Cl₂/10 % NaHSO₄ (4.5:1.5:4); e) PPTS, CH₂Cl₂/MeOH (1:1); 52 % (three steps); f) TBDPSCl, Im, DMAP, CH₂Cl₂; 90 %; g) DDQ, CH₂Cl₂/pH 7 buffer (6:1); 90 %; h) TESCl, Im, CH₂Cl₂; 100 %; i) LiDBB, THF, −78 °C; 85 %; j) SO₃·Py, Et₃N, CH₂Cl₂/DMSO (1:1); k) sulfone **22**, LiHMDS, THF, −78 °C→0 °C; 72 % (two steps); l) Boc₂O, DMAP, CH₃CN; 91 %; m) LiOH, H₂O₂, THF/H₂O (3:1); n) trichlorobenzoyl chloride, *i*Pr₂NEt, then DMAP, toluene; RT; o) PPTS, CH₂Cl₂/MeOH (1:1); 35 % (three steps); p) Dess–Martin periodinane, py, CH₂Cl₂; 72 %; q) TAS-F, H₂O, DMF; 85 %. See reference [5] for abbreviations.

(TBDPSCI, Im, DMAP, CH₂Cl₂, 90 %), exchange of the C14 hydroxy protecting group (DDQ, CH₂Cl₂/pH 7 buffer, 90 %; TESCl, Im, CH₂Cl₂, 100 %), and benzyl deprotection^[16] (LiDBB, THF, −78 °C) afforded **27**, the fully elaborated precursor needed for the diene formation step.

On the basis of convergency considerations the C1–C30 ABCDE fragment **27** was employed as the electrophilic partner in the Julia olefination with the β-alkoxy sulfone **22**.^[21] Oxidation^[22] of alcohol **27** to aldehyde **28** (SO₃·Py, Et₃N, DMSO/CH₂Cl₂) was followed by the addition of LiHMDS to a pre-mixed solution of **28** and sulfone **22** in THF at −78 °C to provide the desired diene **29** as a 88:12 mixture of C32 epimers (72 % over two steps, *E:Z* > 95:5).^[23] Pursuant to revealing the terminal carboxyl residue, *N*-phenylamide **29** was activated through its *N*-Boc imide, and hydrolysis to the acid (LiOH, H₂O₂, THF/H₂O) proceeded with concomitant C33-OTMS deprotection to give pectenotoxin-4 *seco* acid.^[24] Macrocyclization under Yamaguchi conditions^[25] (2,4,6-trichlorobenzoyl chloride, *i*Pr₂NEt, toluene, then DMAP, toluene) at room temperature provided adduct **30**. Selective deprotection of the C14 and C36 OTES ethers with PPTS in MeOH/CH₂Cl₂ (35 % over three steps), oxidation to the diketone^[8] (Dess–Martin periodinane, py, CH₂Cl₂, 72 %) and global deprotection^[26] (TAS-F, H₂O, DMF, 85 %) afforded pectenotoxin-4 in 36 steps (longest linear sequence) and 0.3 % overall yield. The synthetic material was identical by ¹H NMR spectroscopy and optical rotation to natural pectenotoxin-4.^[27] Further proof of structure was obtained by isomerizing synthetic pectenotoxin-4 to pectenotoxin-8^[28] (1 % TFA in CH₃CN/H₂O, 40 %), and this material was identical to natural pectenotoxin-8 as judged by ¹H NMR, HPLC, TLC R_f, and UV spectroscopy.

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