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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**

David A. Evans,* Hemaka A. Rajapakse, Anna Chiu, and Dirk Stenkamp

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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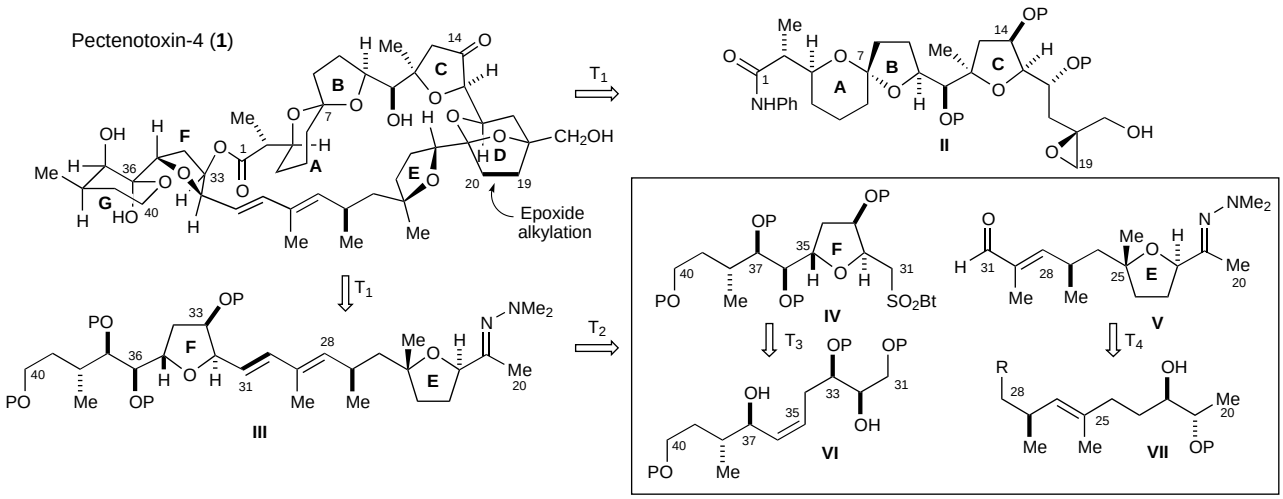
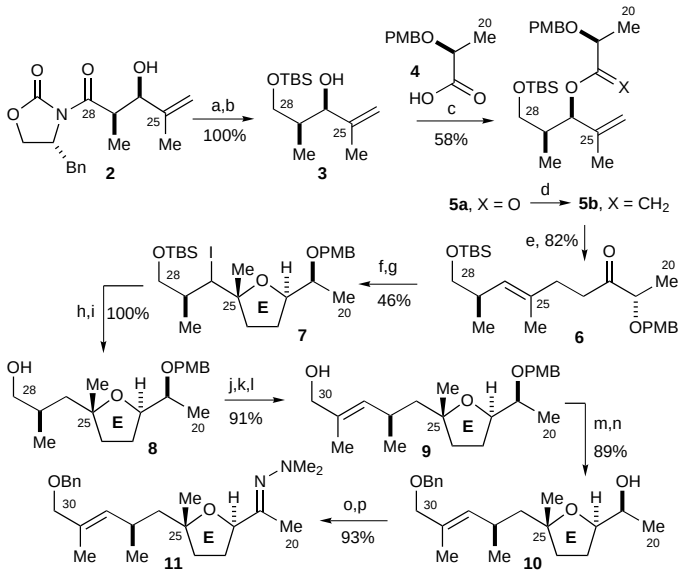


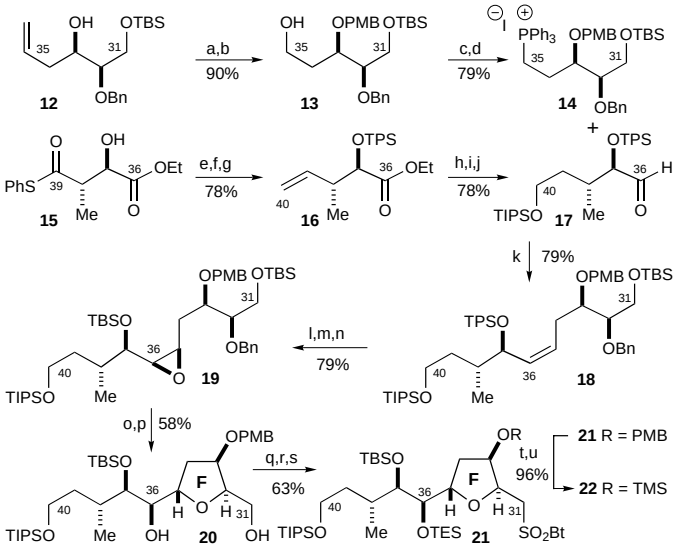
Figure 1. The major disconnections.



Scheme 1. Synthesis of C20–C30 E-ring fragment. a) $LiBH_4$, THF, 0 °C; b) TBSCl, Im, CH_2Cl_2; 100 % (two steps); c) DCC, DMAP, CH_2Cl_2; 52 %; d) $[Cp_2TiCl_2]$, $AlMe_3$, THF, then **5a**; e) toluene, 110 °C; 82 % (two steps); f) $Zn(BH_4)_2$, Et_2O, −78 °C; 74 %; g) NIS, CH_3CN, −40 °C; 64 %; h) Bu_3SnH, AIBN, toluene; 100 %; i) TBAF, THF; 95 %; j) Dess–Martin periodinane, py, CH_2Cl_2; 99 %; k) $EtOC(O)CC(CH_3)PPh_3$, THF, 65 °C; 100 %; l) $LiAlH_4$, Et_2O, 0 °C; 92 %; m) NaH, BnBr, TBAI, THF/DMF (3:1); 94 %; n) DDQ, CH_2Cl_2/pH 7 buffer (8:1); 95 %; o) Dess–Martin periodinane, py, CH_2Cl_2; 93 %; p) TMSCl, CH_2Cl_2/Me_2NNH_2 (1:1), 0 °C; 100 %. See reference [5] for abbreviations.

catalyzed hydroboration[14] ([$(Ph_3P)_3RhCl$], catecholborane, THF, 0 °C, then H_2O_2, EtOH, pH 7 buffer, 88 %), TIPS protection of the resulting primary alcohol (TIPSOTf, lut., CH_2Cl_2, −78 °C, 100 %), and half reduction of the ethyl ester (DIBAL-H, toluene, −78 °C, 89 %) completed the synthesis of aldehyde **17**.

Wittig coupling of phosphonium salt **14** and aldehyde **17** proceeded smoothly (LiHMDS, THF, −78 °C, 79 %, $Z:E$ > 95:5) to afford **18**. Selective deprotection of the TPS ether under basic conditions (K_2CO_3, MeOH/CH_2Cl_2, 87 %), directed epoxidation with *m*-CPBA[15] (CH_2Cl_2, 0 °C, 95 %, d.r. > 95:5) and reprotection of the hydroxy group at C37 as a TBS ether (TBSOTf, lut., CH_2Cl_2, −78 °C, 95 %) afforded epoxide **19** as a single diastereomer. Selective deprotection of the benzyl ether group at C32 was possible under reducing conditions.[16] When the resulting epoxy alcohol was exposed to PPTS in MeOH/CH_2Cl_2, cyclization to form the F-ring tetrahydrofuran with simultaneous deprotection of the C31-OTBS ether afforded diol **20** in 73 % yield.[17] Installation of the benzthiazole sulfide at C31 under Mitsunobo conditions (BtSH, DIAD, Ph_3P, THF, 0 °C), oxidation to the sulfone[18]



Scheme 2. C31–C40 FG fragment synthesis. a) PMBBr, NaH, THF/DMF (3:1), 0 °C; 95 %; b) O_3, EtOH, −78 °C, then DMS, then $NaBH_4$; 95 %; c) I_2, Im, Ph_3P, CH_2Cl_2, 0 °C; 89 %; d) Ph_3P, CH_3CN, 55 °C, 89 %; e) TPSCl, Im, DMAP, DMF, 0 °C; 98 %; f) Pd/C, Et_3SiH, acetone; 95 %; g) $[Cp_2ZrCl_2]$, Zn dust, CH_2I_2, THF, 0 °C; 84 %; h) $[(Ph_3P)_3RhCl]$, catecholborane, THF, then pH 7 buffer, H_2O_2; 88 %; i) TIPSOTf, lut., CH_2Cl_2, −78 °C; 100 %; j) DIBAL-H, toluene, −78 °C; 89 %; k) LiHMDS, THF, then aldehyde **17**, −78 °C→0 °C; 79 %; l) K_2CO_3, MeOH/CH_2Cl_2 (2:1); 87 %; m) *m*-CPBA, CH_2Cl_2, 0 °C; 95 %; n) TBSOTf, lut., CH_2Cl_2, −78 °C; 95 %; o) LiDBB, THF, −78 °C; 79 %; p) PPTS, MeOH/CH_2Cl_2 (1:1); 73 %; q) BtSH, Ph_3P, DIAD, THF, 0 °C; r) *m*-CPBA, CH_2Cl_2, 0 °C; 70 % (two steps); s) TESCl, Im, CH_2Cl_2; 90 %; t) DDQ, CH_2Cl_2/pH 7 buffer (10:1); 97 %; u) TMSCl, Im, CH_2Cl_2, 99 %. See reference [5] for abbreviations.

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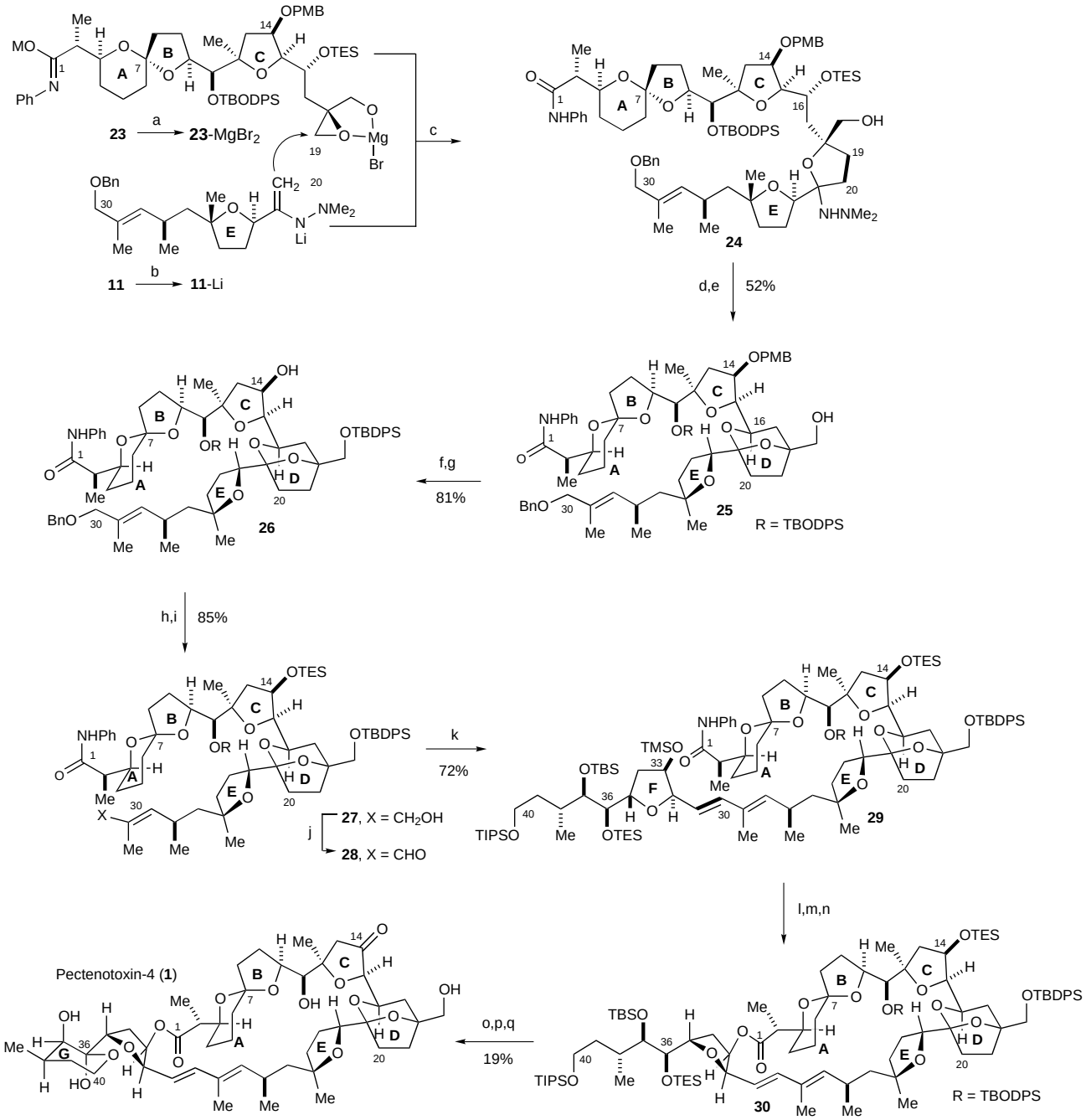
(*m*-CPBA, CH_2Cl_2, 0 °C, 70 % over two steps), and protection of the hydroxy group at C36 as a TES ether (TESCl, Im, CH_2Cl_2, 90 %) afforded **21**. In preparation for the diene formation step, the C33-OPMB ether of sulfone **21** was exchanged for the corresponding TMS ether (DDQ, CH_2Cl_2/pH 7 buffer, 97 %; then TMSCl, Im, CH_2Cl_2, 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**-$MgBr_2$[20] to the metalloenamine derived from **11**. The resulting unstable hydrazinyl lactol **24** was treated with acid under biphasic conditions (pentane/CH_2Cl_2/10 % aq. $NaHSO_4$) 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/CH_2Cl_2 (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**-$MgBr_2$ to **11**-Li, +10 °C; d) pentane/CH_2Cl_2/10 % $NaHSO_4$ (4.5:1.5:4); e) PPTS, CH_2Cl_2/MeOH (1:1); 52 % (three steps); f) TBDPSCl, Im, DMAP, CH_2Cl_2; 90 %; g) DDQ, CH_2Cl_2/pH 7 buffer (6:1); 90 %; h) TESCl, Im, CH_2Cl_2; 100 %; i) LiDBB, THF, −78 °C; 85 %; j) SO_3·Py, Et_3N, CH_2Cl_2/DMSO (1:1); k) sulfone **22**, LiHMDS, THF, −78 °C→0 °C; 72 % (two steps); l) Boc_2O, DMAP, CH_3CN; 91 %; m) LiOH, H_2O_2, THF/H_2O (3:1); n) trichorobenzoyl chloride, *i*Pr_2NEt, then DMAP, toluene; RT; o) PPTS, CH_2Cl_2/MeOH (1:1); 35 % (three steps); p) Dess–Martin periodinane, py, CH_2Cl_2; 72 %; q) TAS-F, H_2O, DMF; 85 %. See reference [5] for abbreviations.

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(TBDPSCl, Im, DMAP, CH_2Cl_2, 90%), exchange of the C14 hydroxy protecting group (DDQ, CH_2Cl_2/pH 7 buffer, 90%; TESCl, Im, CH_2Cl_2, 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** (SO_3·Py, Et_3N, DMSO/CH_2Cl_2) 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, H_2O_2, THF/H_2O) proceeded with with concomitant C33-OTMS deprotection to give pectenotoxin-4 *seco* acid.[24] Macrocyclization under Yamagichi conditions[25] (2,4,6-trichlorobenzoyl chloride, *i*Pr_2NEt, toluene, then DMAP, toluene) at room temperature provided adduct **30**. Selective deprotection of the C14 and C36 OTES ethers with PPTS in MeOH/CH_2Cl_2 (35% over three steps), oxidation to the diketone[8] (Dess–Martin periodinane, py, CH_2Cl_2, 72%) and global deprotection[26] (TAS-F, H_2O, DMF, 85%) afforded pectenotoxin-4 in 36 steps (longest linear sequence) and 0.3% overall yield. The synthetic material was identical by ^{1}H 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 CH_3CN/H_2O, 40%), and this material was identical to natural pectenotoxin-8 as judged by ^{1}H NMR, HPLC, TLC R_f, and UV spectroscopy.

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[5] Abbreviations: TBS = *tert*-butyldimethylsilyl; DCC = dicyclohexyl carbodiimide; DMAP = 4-(*N*,*N*-dimethylamino)pyridine; Cp = cyclopentadienyl, d.r. = diastereomeric ratio; NIS = *N*-iodosuccinimide; AIBN = 2,2′-azobisisobutyronitrile; TBAF = tetra-(*n*-butyl)ammonium fluoride; THF = tetrahydrofuran; py = pyridine; Bn = benzyl; TBAI = tetra-(*n*-butyl)ammonium iodide; DMF = dimethylformamide; DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; TMS = trimethylsilyl; DMS = dimethyl sulfide; Im = imidazole; TPS = triphenylsilyl; TIPS = triisopropylsilyl; lut. = 2,6-lutidine; DIBAL-H = diisobutylaluminum hydride; LiHMDS = lithium hexamethyldisilazide; *m*-CPBA = *meta*-chloroperoxybenzoic acid; Bt = benzthiazole; TES = triethylsilyl; PPTS = pyridinium *para*-toluenesulfonate; TBDPS = *tert*-butyldiphenylsilyl; LiDBB = lithium di-*tert*-butylbiphenylide; Boc_2O = di-*tert*-butyl dicarbonate; LDA = lithium diisopropylamide; HMPA = hexamethylphosphoramide; TBODPS = *tert*-butoxydiphenylsilyl; RT = room temperature; TAS-F = tris(dimethyamino)sulfur(trimethylsilyl)difluoride.

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