Natural Products Synthesis

A Formal Total Synthesis of (+)-Pinnatoxin A[**]

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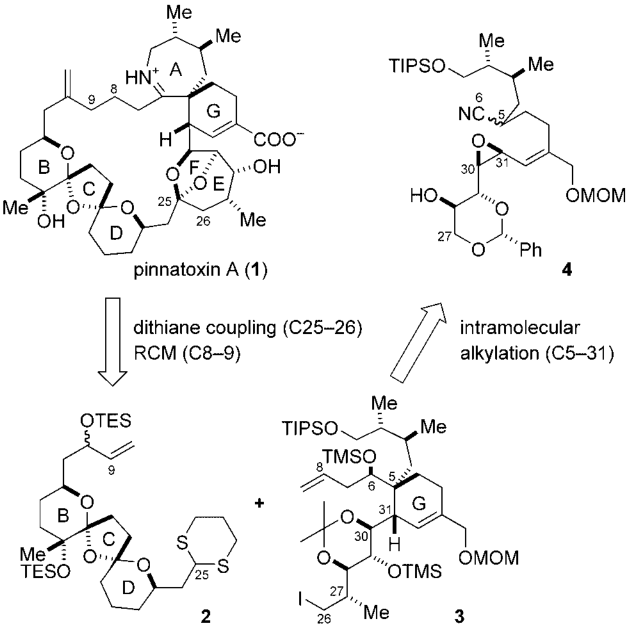
In 1995, Uemura and co-workers reported the isolation and characterization of pinnatoxin A (**1**, Scheme 1),[1,2] one of the major toxic principles responsible for outbreaks of *Pinna* shellfish poisonings in China and Japan. The precise biological activity has not been clarified, but **1** has been suggested to be a Ca^{2+}-channel activator.[3] Structurally, **1** features a spiro-linked cyclic imine along with trioxadispiro- and bicycloacetal substructures within a 27-membered macrocycle. The novel chemical and biological aspects of **1** render it an intriguing and challenging target. Indeed, a number of synthetic approaches have been described to date.[4–6] The only total synthesis of **1** was reported by Kishi in 1998,[7] an achievement further highlighted by the determination of the absolute configuration of **1** and the development of a biomimetic intramolecular Diels–Alder reaction to construct the G ring along with the macrocycle. Herein, we describe our own efforts in this area which have culminated in a formal total synthesis of natural (+)-pinnatoxin A.

Our synthetic strategy toward (+)-**1** targeted an optimally convergent route in which two complex fragments (**2** and **3**) were to be constructed, coupled, and elaborated to form the macrocyclic system (Scheme 1). We envisaged assembling **2** and **3** through a dithiane coupling reaction at C25; the polyether macrocycle would then emerge from ring-closing olefin metathesis reaction (RCM)[8] to link C8 and C9, and subsequent EF-ring formation. Ring G was to be constructed by using intramolecular cyclization of epoxy nitrile **4**,[9] which would set the stereochemistry of the C5 quaternary center, as demonstrated in our model studies on simple substrates.[4c,d]



Scheme 1. Retrosynthesis of pinnatoxin A. MOM = methoxymethyl; TES = triethylsilyl; TIPS = triisopropylsilyl; TMS = trimethylsilyl.

The synthesis of the BCD bisspiroacetal **2** began with previously reported compound **5**[4a] (Scheme 2). Sharpless asymmetric epoxidation[10] of allylic alcohol **5** with (+)-diethyl tartrate provided **6**. Oxidation of alcohol **6** to aldehyde **7** with SO_3·py/DMSO followed by treatment with vinylmagnesium bromide produced epoxy alcohol **8** as a 1:1 diastereomeric mixture. Subsequent reductive opening of epoxide **8** with Red-Al in Et_2O resulted in the formation of 1,3-diol **9** as the major isomer.[11] After protection of **9** as its acetonide, chemo- and enantioselective dihydroxylation of the C15–C16 olefin was realized under Sharpless conditions in the presence of $(DHQD)_2PHAL$,[12] which exclusively produced the desired

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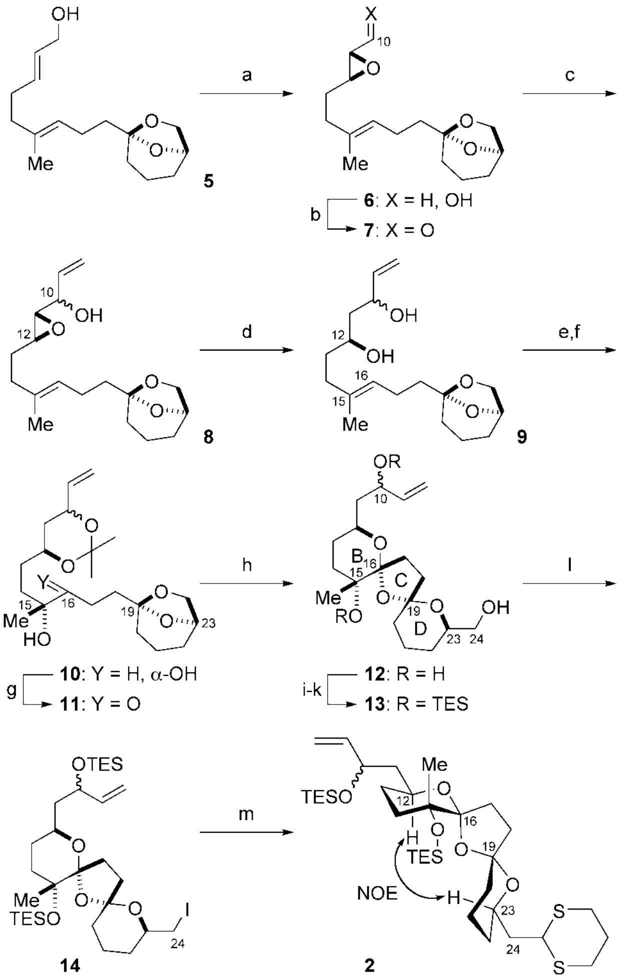


Scheme 2. Reagents and conditions: a) *t*BuOOH, Ti(O*i*Pr)$_4$ (0.2 equiv), (+)-DET (0.2 equiv), molecular sieves (4 Å), CH_2Cl_2, −20 °C, 83 %; b) SO_3·py, Et_3N, DMSO, CH_2Cl_2, room temperature; c) CH_2=CHMgBr, THF, −40 °C, 74 % (over two steps); d) $NaAlH_2(OCH_2CH_2OCH_3)_2$, Et_2O, −20→0 °C; then $NaIO_4$, THF/H_2O (1:1), room temperature, 90 %; e) 2-methoxypropene, *p*-TsOH, DMF, room temperature, 91 %; f) OsO_4 (1 mol %), (DHQD)$_2$PHAL (1.5 mol %), $K_3[Fe(CN)_6]$ (3 equiv), K_2CO_3 (3.5 equiv), $MeSO_2NH_2$ (1 equiv), *t*BuOH/H_2O (1:1), 0 °C; g) SO_3·py, Et_3N, DMSO, room temperature, 82 % (over two steps); h) CSA (0.1 equiv), MeOH, room temperature, 3 h; then CSA, toluene, room temperature, 2 days, 84 % (**12**), 11 % (C19-epimer); i) PivCl, CH_2Cl_2/pyridine (2:1), 0 °C→RT; j) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; k) DIBAL-H, THF, −78 °C, 75 % (over three steps); l) I_2, Ph_3P, imidazole, THF, room temperature, 91 %; m) 1,3-dithiane, *n*BuLi, THF/HMPA (4:1), −78 °C, 83 %. DET = diethyl tartrate; DMSO = dimethyl sulfoxide; Ts = *p*-toluenesulfonyl; DMF = *N*,*N*-dimethylformamide; (DHQD)$_2$PHAL = hydroquinidine 1,4-phthalazinediyl diether; CSA = (+)-camphorsulfonic acid; Piv = pivaloyl; Tf = trifluoromethanesulfonyl; DIBAL-H = diisobutylaluminum hydride; HMPA = hexamethylphosphoramide.

1,2-diol **10** without oxidizing the terminal olefin. Then, oxidation with SO_3·py converted secondary alcohol **10** into ketone **11**.

The crucial bisspiroacetalization of **11** necessitated fine-tuning of the reaction conditions.[13] First, **11** was exposed to camphorsulfonic acid in methanol at room temperature to remove the acetonide, and then methanol was replaced with toluene to increase the ratio of the desired isomer **12**. In this way, **12** was selectively generated out of four possible isomers in 84 % yield. As depicted in Figure 1, favorable intramolecular hydrogen bonding between free hydroxy groups at C10 and C24 is considered to influence the high selectivity for **12**.[14] Next, the 10-OH and 15-OH groups of **12** were protected as their TES ethers through a three-step sequence to afford **13**, whose 24-OH function was converted into iodide to give **14**. Finally, nucleophilic attack of lithiodithiane at **14** delivered the BCD-ring fragment **2**, suitably functionalized for assembly of the fragments. The configurations of the C16 and C19 stereocenters established during the spiroacetalization were unambiguously determined by NOE experiments at this stage.

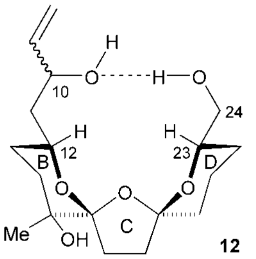
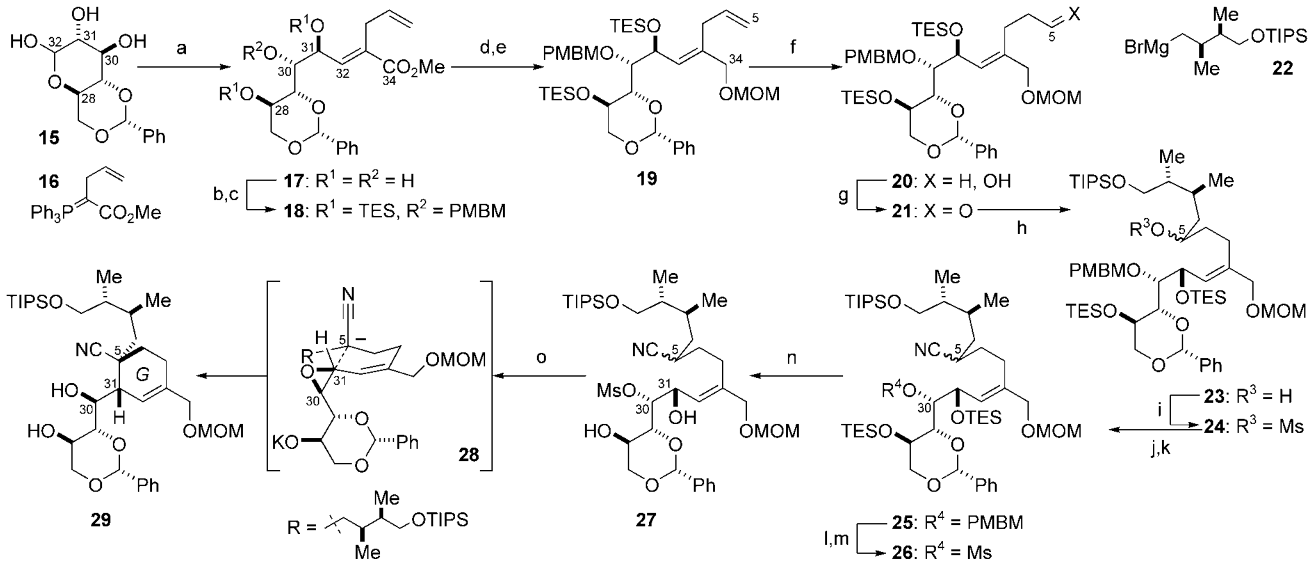


Figure 1. Potential intramolecular hydrogen bond in **12**.

Synthesis of the other half of the molecule began with 4,6-*O*-benzylidene-D-glucose (**15**)[15] (Scheme 3). Wittig reaction of **15** with ylide **16**[16] in refluxing THF afforded olefin (*E*)-**17**. The hydroxy groups at C28 and C31 of **17** were selectively protected as TES ethers, and PMBM[17] was introduced to protect the remaining 30-OH to produce **18**. Reduction with DIBAL-H and subsequent protection with MOMCl converted ester **18** into MOM ether **19**. Then, chemoselective hydroboration[18] of the terminal olefin of diene **19** generated alcohol **20**, which was oxidized to aldehyde **21** with SO_3·py. Addition of Grignard reagent **22**[4d] to **21** extended the carbon chain corresponding to the A-ring to furnish **23**. The secondary alcohol of **23** was derivatized to mesylate **24**, after which the mesylate was replaced by a nitrile group through the action of Et_4NCN to provide **25** after reattachment of the partially cleaved TES groups (1:1 diastereomeric mixture at C5). Replacement of the PMBM group of **25** with the Ms group in two steps and subsequent selective removal of TES from **26** with HF·py resulted in diol **27**.

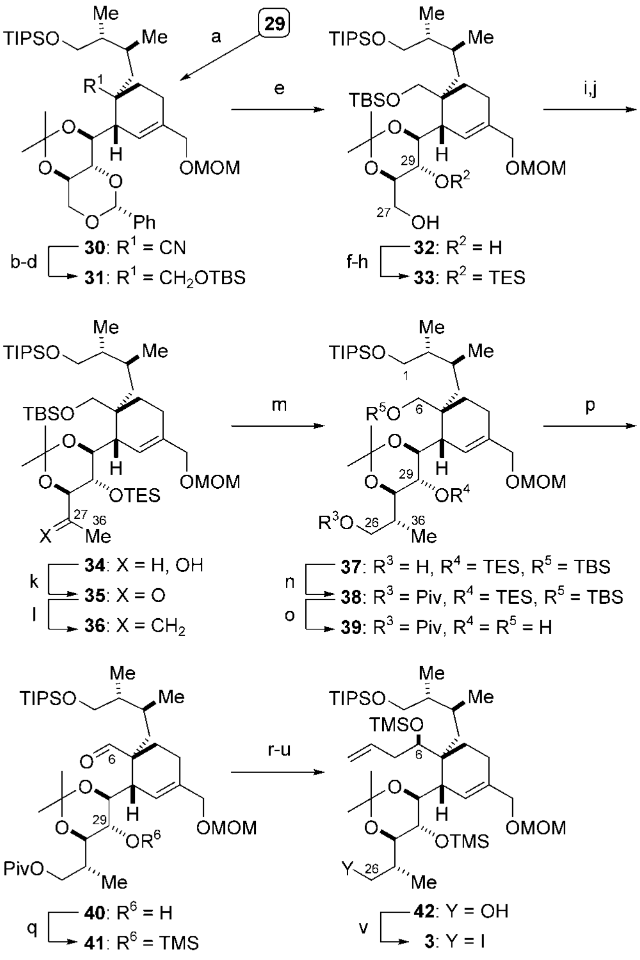
Stereoselective G-ring formation from **27** was induced by an excess of KN(TMS)$_2$.[4c,d] After treating mesylate **27** with KN(TMS)$_2$ (2.5 equiv) in THF to promote the C30–C31 epoxide formation,[19] additional KN(TMS)$_2$ (1.5 equiv) was introduced to the reaction mixture, giving rise to the desired product **29** as the sole isomer in 72 % yield.[20] Not only is the stereoselectivity quite remarkable, but the reactions efficiently install consecutive C5 quaternary and C31 tertiary centers. The selectivity is consistent with cyclization through transition state **28** in which the large branched carbon chain preferentially adopts the equatorial orientation.

Having constructed the G-ring, we turned our attention to stereoselective introduction of the C36-methyl group and



Scheme 3. Reagents and conditions: a) **16** (2 equiv), THF, reflux; b) TESCl, Et_3N, THF, 40 °C; c) PMBMCl, $i$$Pr_2NEt$, $n$$Bu_4NBr$, CH_2Cl_2, reflux, 51% (over three steps); d) DIBAL-H, THF, −78 °C, 89%; e) MOMCl, $i$$Pr_2NEt$, $n$$Bu_4NBr$, $(CH_2Cl)_2$, room temperature, 95%; f) 9-BBN, THF, room temperature; then aqueous H_2O_2, aqueous NaOH, 0 °C→RT, 90%; g) SO_3·py, Et_3N, DMSO, CH_2Cl_2, room temperature, 84%; h) **22** (2.5 equiv), THF, 0 °C, 85%; i) MsCl, Et_3N, CH_2Cl_2, 0 °C; j) Et_4NCN, MeCN, 70 °C; k) TESCl, imidazole, DMF, room temperature, 67% (over three steps); l) DDQ, CH_2Cl_2/pH 7 buffer (20:1), 85%; m) MsCl, DMAP, pyridine, 40 °C; n) HF·py, 0 °C, 99% (over two steps); o) $KN(TMS)_2$ (2.5 equiv), THF, 0 °C; then $KN(TMS)_2$ (1.5 equiv), 0 °C→RT, 72%. PMBM = p-methoxybenzyloxymethyl; 9-BBN = 9-borabicyclo[3.3.1]nonane; Ms = methanesulfonyl; DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; DMAP = 4-(dimethylamino)pyridine.

elongation of the carbon chain at C6 (Scheme 4). First, 1,3-diol **29** was converted into acetonide **30**, of which stepwise reduction to the alcohol and subsequent protection with TBS afforded **31**. Then, deprotection of the benzylidene acetal of **31** under Birch conditions produced diol **32**, and the secondary alcohol at C29 was quantitatively protected as its TES ether to give **33** in a three-step sequence. Oxidation of the remained primary alcohol of **33** with SO_3·py followed by addition of MeMgBr led to secondary alcohol **34**, which was further oxidized to ketone **35**. Treatment of **35** with the Tebbe reagent[21] resulted in exo olefin **36**. Regio- and stereoselective hydroboration of diene **36** was realized with 9-BBN to generate **37** with the desired C36-methyl stereochemis-



Scheme 4. Reagents and conditions: a) 2,2-dimethoxypropane, CSA, CH_2Cl_2, room temperature, 88%; b) DIBAL-H, toluene, −30 °C→RT; then SiO_2, hexane, room temperature, 99%; c) DIBAL-H, toluene, −78 °C to 0 °C; d) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 100% (2 steps); e) Na, liq NH_3, THF, −78 °C, 91%; f) PivCl, pyridine, room temperature; g) TESCl, imidazole, DMF, room temperature; h) DIBAL-H, toluene, −78 °C, 100% (over three steps); i) SO_3·pyridine, DMSO, Et_3N, CH_2Cl_2, room temperature; j) MeMgBr, THF, 0 °C; k) Dess–Martin periodinane, CH_2Cl_2/pyridine (5:1), room temperature, 87% (over three steps); l) Tebbe reagent, THF, room temperature, 95%; m) 9-BBN, THF, room temperature; then aqueous H_2O_2, aqueous NaOH, 0 °C→RT, 78%; n) PivCl, DMAP, pyridine, room temperature; o) TBAF, THF, room temperature, 100% (over two steps); p) PDC, CH_2Cl_2, room temperature, 84%; q) TMSCl, imidazole, DMF, room temperature, 94%; r) $CH_2{=}CHCH_2MgBr$, THF, 0 °C; s) PivCl, DMAP, pyridine, room temperature; t) TMSCl, imidazole, DMF, room temperature; u) DIBAL-H, toluene, −78 °C, 67% (**42**, over four steps), 17% (C6-epimer, over four steps); v) I_2, Ph_3P, imidazole, THF, room temperature, 88%. TBS = *tert*-butyldimethylsilyl; TBAF = tetrabutylammonium fluoride; PDC = pyridinium dichromate.

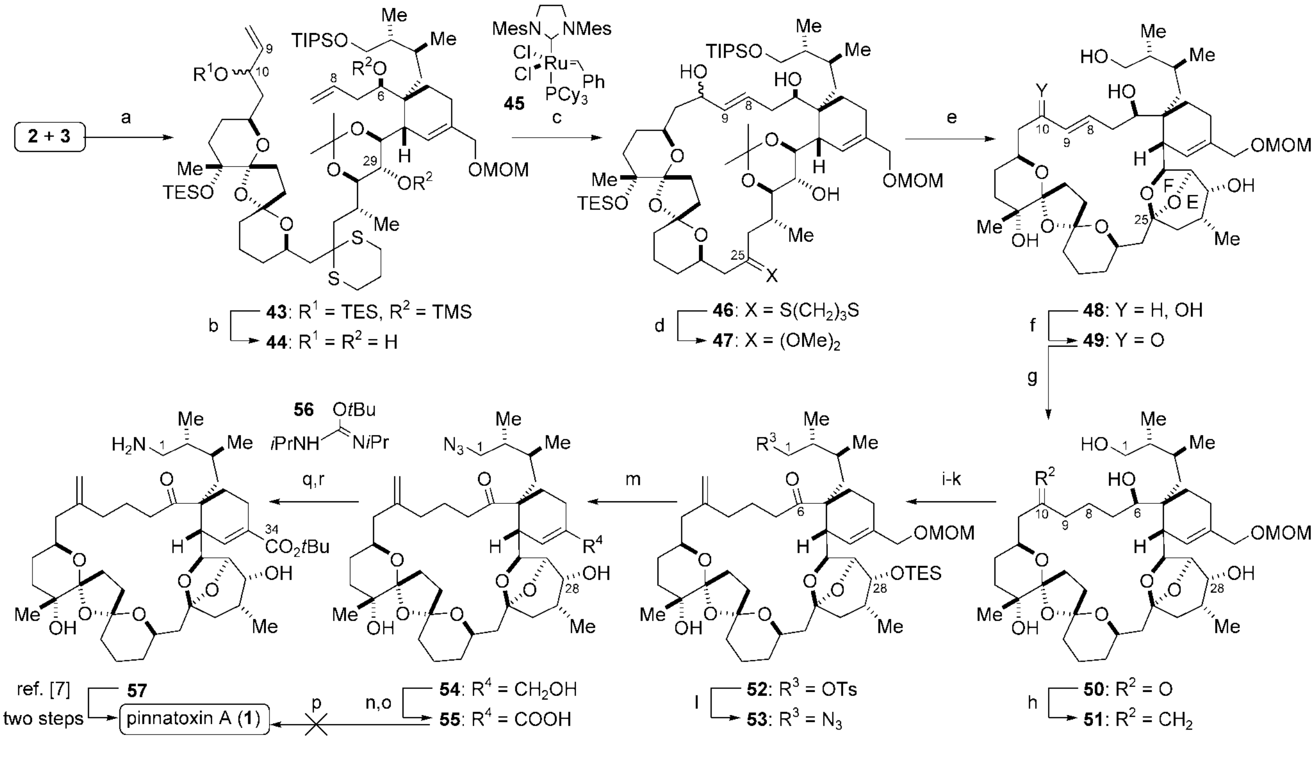
try.[22] Primary alcohol **37** was in turn transformed into pivaloyl ester **38**, from which the silyl protecting groups (except TIPS) were removed with TBAF to afford **39**. After selective oxidation of diol **39** with PDC to form aldehyde **40**, the 29-OH group was converted into the TMS ether to afford **41**. Addition of allylmagnesium bromide to the C6 aldehyde of **41** and a subsequent reprotection–deprotection sequence gave **42**. Lastly, introduction of iodine at C26 of alcohol **42** furnished **3**, appropriately functionalized for the next coupling reaction.

The stage was now set for union of the two highly complex structural fragments **2** and **3** and subsequent macrocyclization by RCM (Scheme 5). Lithiation of dithiane **2** with *t*BuLi in THF/HMPA at −78 °C was immediately followed by addition of a precooled solution of iodide **3**,[23] delivering the coupling adduct **43** in 95 % yield based on recovered **3**. After many unsuccessful attempts to effect the macrocyclization of **44**, it was found that the silyl protecting groups proximal to the terminal olefins impeded the RCM reaction, presumably owing to steric shielding of the reaction sites. Therefore, the TES (10-OH) and two TMS groups (6-, 29-OH) were selectively removed with TBAF at 0 °C to produce triol **44**. Gratifyingly, macro-RCM reaction of **44** was enabled by the action of Grubbs catalyst **45**,[24] resulting in the formation of 27-membered carbocycle **46** with the *E* olefin (75 % yield).

Prior to construction of the EF-ring system within the obtained macrocycle, dithiane **46** was transformed into dimethyl acetal **47** with the Stork reagent (($(CF_3CO_2)_2IPh$, MeOH).[25] Then, **47** was sequentially subjected to TFA/MeOH and CSA/MeOH,[26] which led to deprotection of the acetonide and silyl protecting groups, and concomitant cyclization of the desired EF-ring of **48** in 71 % yield over the sequence. Notably, the preexisting trioxadispiroacetal moiety was left intact under these acidic conditions.

With the synthesis of the entire macrocyclic structure of **1** completed, the end game for the total synthesis entailed specific functional-group manipulations of the highly complicated molecule. The C10 allylic alcohol of pentaol **48** was oxidized with DDQ to afford α,β-unsaturated ketone **49**,[27] which was converted into ketone **50** by 1,4-reduction of the C8–C9 double bond with the Stryker reagent.[28] The exo methylene group was then introduced at C10 of **50** by Wittig reaction to provide **51**. The Ts and TES groups were sequentially introduced to 1-OH and 28-OH of **51**, respectively, and the 6-OH group was oxidized with Dess–Martin periodinane[29] to give ketone **52**. Displacement of tosylate of **52** with azide generated **53**, which was treated with acid to remove the MOM and TES groups, affording triol **54**. Allylic alcohol **54** was then oxidized to carboxylic acid **55** in a two-step sequence (MnO_2[30] then $NaClO_2$).

To obtain pinnatoxin A (**1**) directly from **55**, intramolecular aza-Wittig reaction of azide **55** was attempted in the presence of PMe_3.[4d] However, **1** was not detected in the reaction products, and the amine was only obtained through



Scheme 5. Reagents and conditions: a) *t*BuLi (1.9 equiv), **2** (1.7 equiv), THF/HMPA (9:1), −78 °C, 95 % based on recovered **3** (41 %); b) TBAF, THF, 0 °C, 89 %; c) **45** (0.1 equiv), CH_2Cl_2, reflux, 75 %; d) $(CF_3CO_2)_2IPh$, molecular sieves (3 Å), MeOH/CH_2Cl_2 (20:9), room temperature; e) TFA/MeOH (1:20), room temperature; then CSA, MeOH, room temperature, 71 % (over two steps); f) DDQ, 1,4-dioxane/CH_2Cl_2 (1:1), 40 °C, 67 %; g) $[\{(Ph_3P)CuH\}_6]$ (0.1 equiv), toluene/H_2O (100:1), room temperature, 64 %; h) Ph_3PCH_3Br, *t*BuOK, THF, 0 °C, 64 %; i) *p*-TsCl, Et_3N, DMAP, molecular sieves (4 Å), CH_2Cl_2, room temperature; j) TESCl, imidazole, CH_2Cl_2, room temperature, 51 % (over two steps); k) Dess–Martin periodinane, CH_2Cl_2; l) NaN_3, DMF, 80 °C, 68 % (over two steps); m) aqueous HCl (2 N)/THF (1:10), 40 °C, 96 %; n) MnO_2, CH_2Cl_2, room temperature; o) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*BuOH/H_2O (4:1), 0 °C; p) PMe_3, THF, 60 °C, 0 % (**1**); q) **56**, toluene, 70 °C, 34 % (over three steps); r) PMe_3, THF/H_2O (10:1), room temperature, 60 %.

hydrolysis of the resultant N=P bond. Therefore, we elected to complete the formal total synthesis of **1** simply by reduction of the C1 azide and esterification of the C34 carboxylic acid. Introduction of *t*Bu to **55** with **56**[31] and subsequent treatment with PMe_3 in THF/H_2O[32] gave rise to amine **57**, which had been transformed into **1** by Kishi in two steps.[33] Our synthetic **57** showed ^{1}H NMR data that was identical to that provided by Professor Kishi.

In summary, we have reported the formal total synthesis of (+)-pinnatoxin A in a highly convergent fashion. The salient methodologies employed in our successful campaign include 1) stereoselective bis-acetalization to yield the BCD-ring fragment **2** effected by exploiting intramolecular hydrogen bonding; 2) intramolecular alkylation of epoxynitrile **4** to construct the G-ring; 3) powerful dithiane coupling to unify the two halves of the molecule (**2** and **3**); 4) macrocyclization of 27-membered carbocycle **46** by utilizing olefin metathesis reaction; and 5) intramolecular acetalization of the complex macrocycle to construct EF-ring **49**.

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