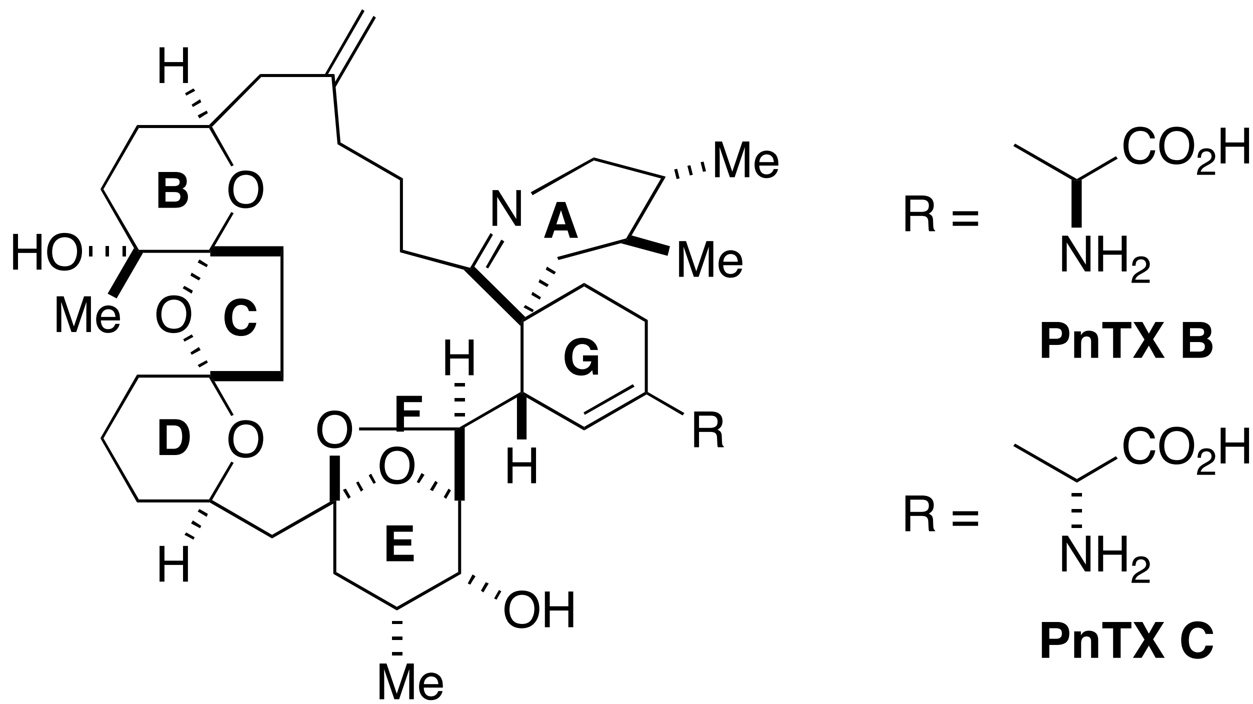
Total Synthesis and Stereochemistry of Pinnatoxins B and C



Matsuura, F.; Hao, J.; Reents, R.; Kishi, Y.
Org. Lett. ASAP

Structures of Pinnatoxins (PnTXs) and Pteriatoxins (PtTXs)

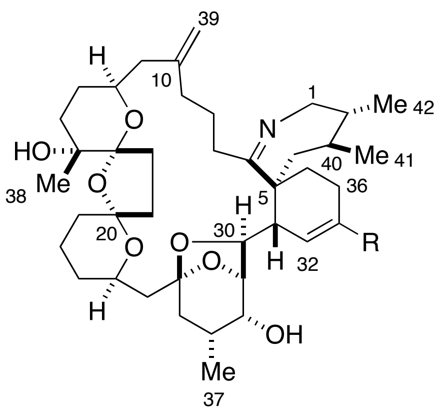
PnTX A - Isolated in 1995 from Pinna muricata

PnTXs B & C - Isolated in 2001

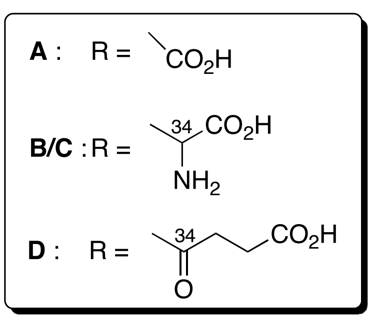
PtTXs A-C - Isolated in 2001 from Pteria penguin

Neurotoxins Responsible for the Pinna Shellfish Poisoning

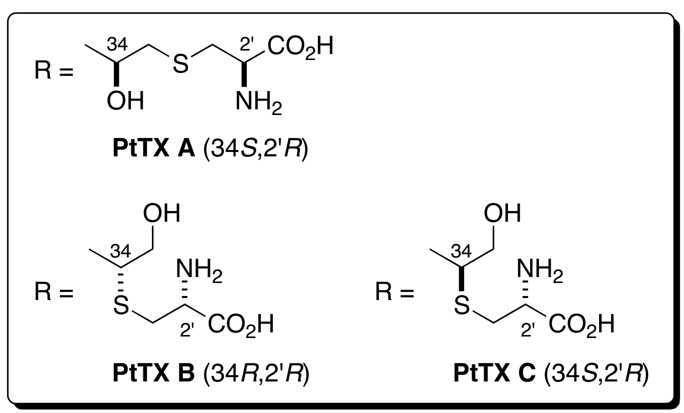
Ca^{2+}-Channel Activator



Pinnatoxins

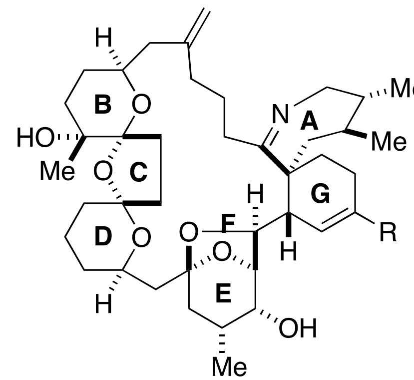


Pteriatoxins



JACS **1995**, *117*, 1155.
TL **1996**, *37*, 4023.
JACS **2006**, *128*, 7742.

Synthesis of Pinnatoxins



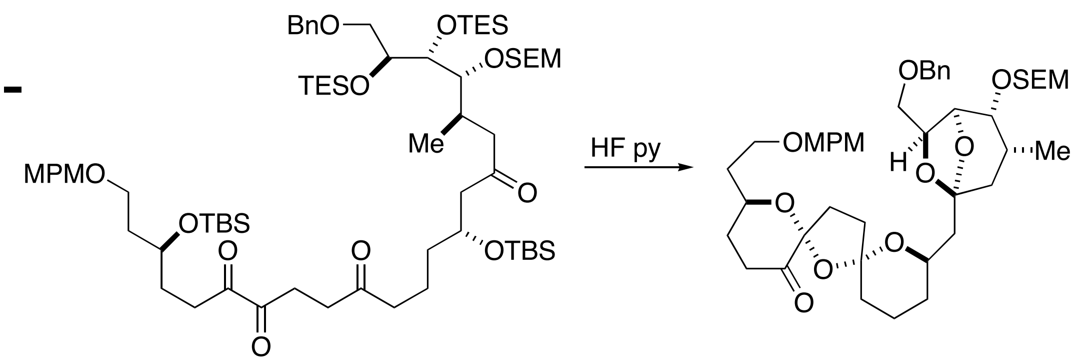
1) Kishi - (-)-PnTX A in 1998 - Biomimetic Intramolecular Diels-Alder Reaction

2) Hirama - Formal Total Synthesis of (+)-PnTX A in 2004

3) Hashimoto - BCDEF Rings by Tandem Double Hemiketal Formation/Intramolecular Hetero-Michael Addition

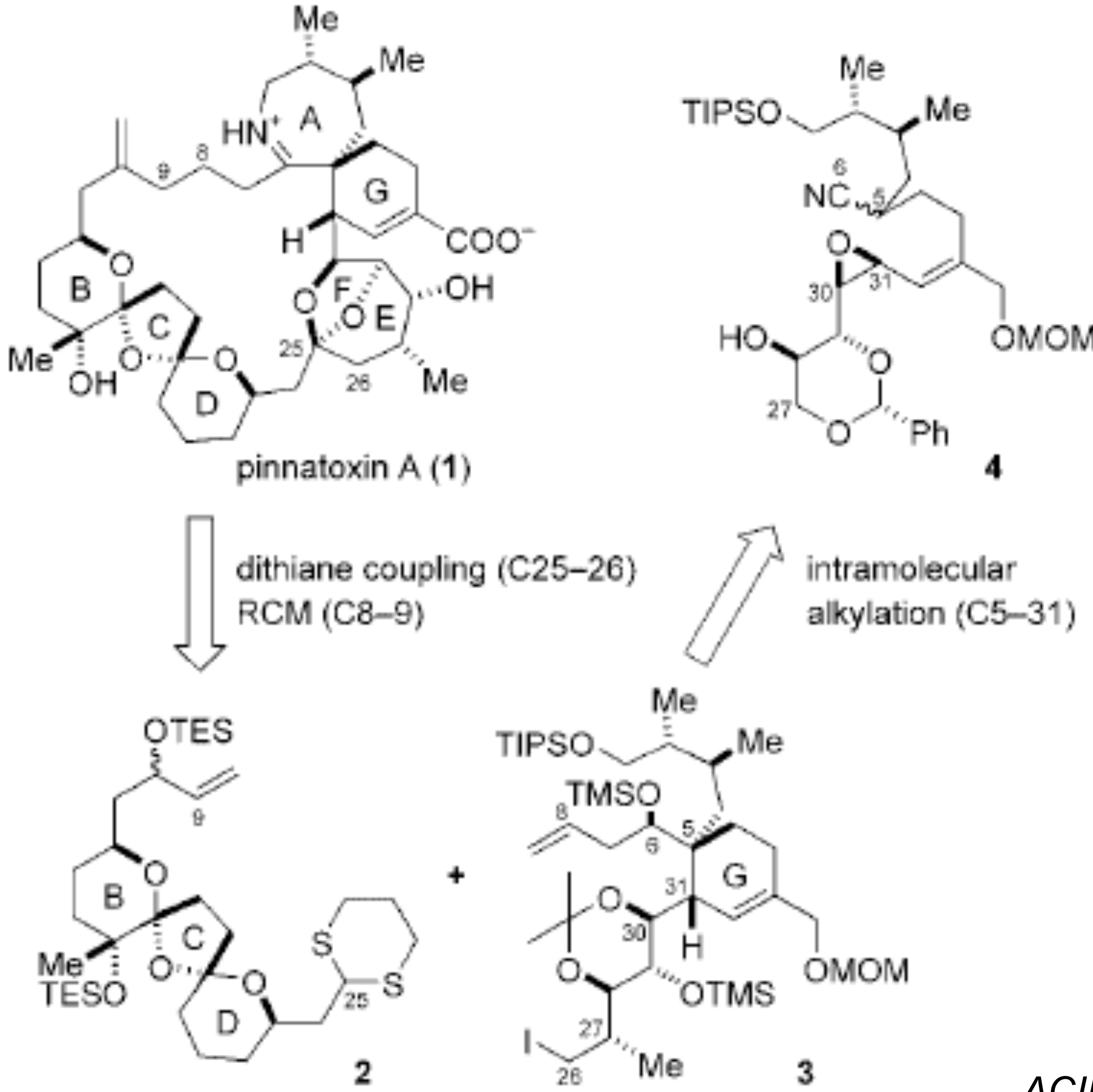
4) Zakarian - AG Rings by Cascade Sigmatropic Rearrangement of Vinylic Sulfoxide

5) Murai -



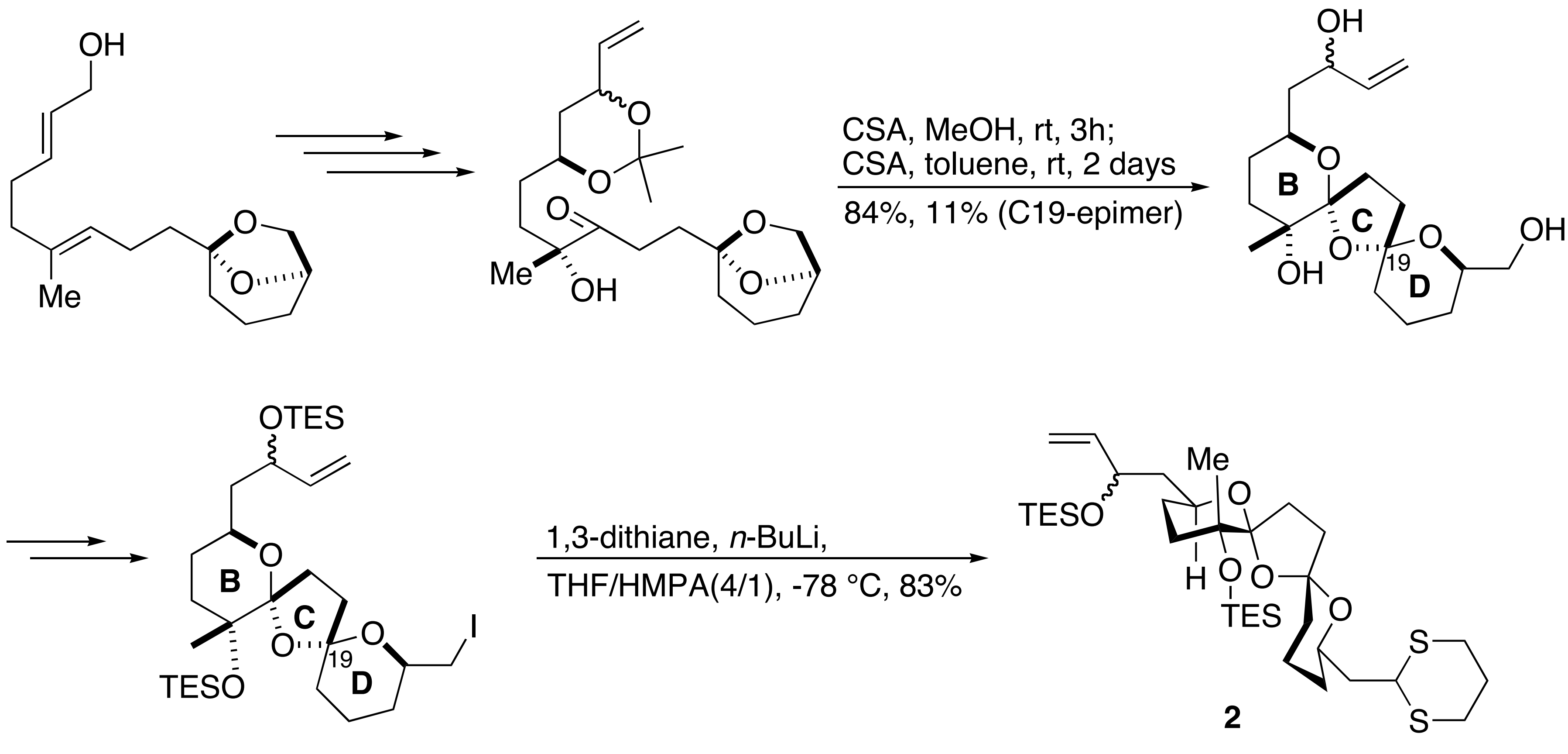
JACS **1998**, *120*, 7647
ACIE **2004**, *43*, 6505
T **2002**, *58*, 10375
OL **2005**, *7*, 1629
CC **2001**, 1392

Retrosynthesis of Pinnatoxin A - Hirama



ACIE **2004**, *43*, 6505

Synthesis of Pinnatoxin A - Hirama



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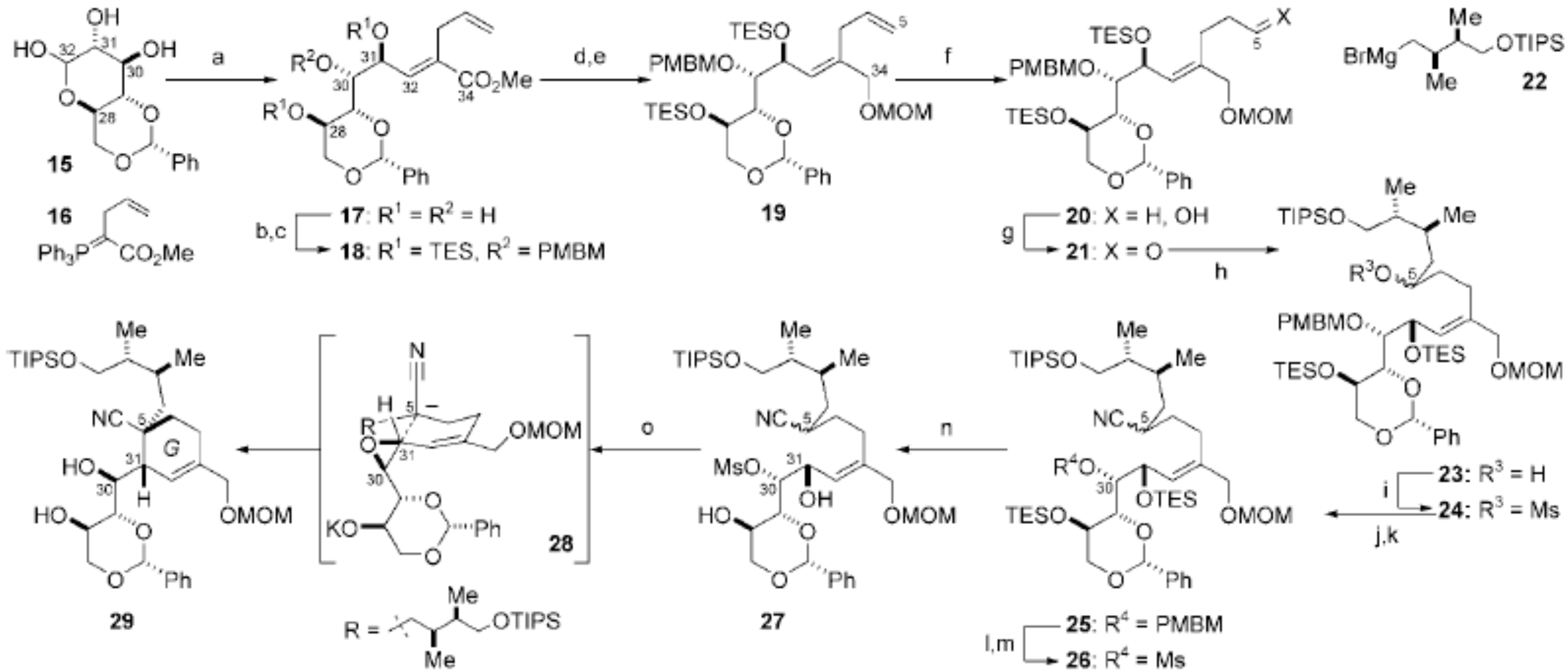
ACIE **2004**, *43*, 6505

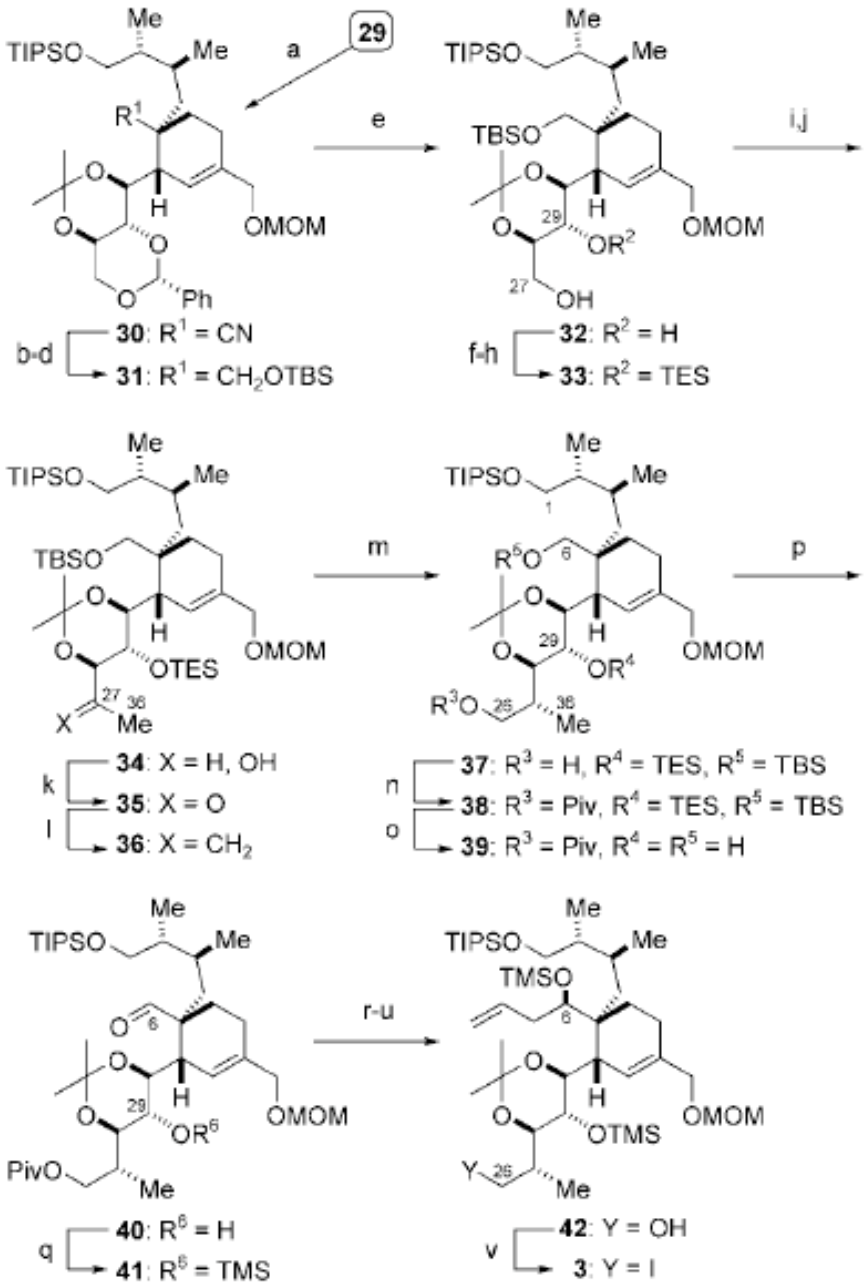
Synthesis of Pinnatoxin A - Hirama



Scheme 3. Reagents and conditions: a) **16** (2 equiv), THF, reflux; b) TESCl, Et_3N, THF, 40 °C; c) PMBMCl, iPr_2NEt, nBu_4NBr, CH_2Cl_2, reflux, 51 % (over three steps); d) DIBAL-H, THF, −78 °C, 89 %; e) MOMCl, iPr_2NEt, nBu_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;

ACIE **2004**, *43*, 6505

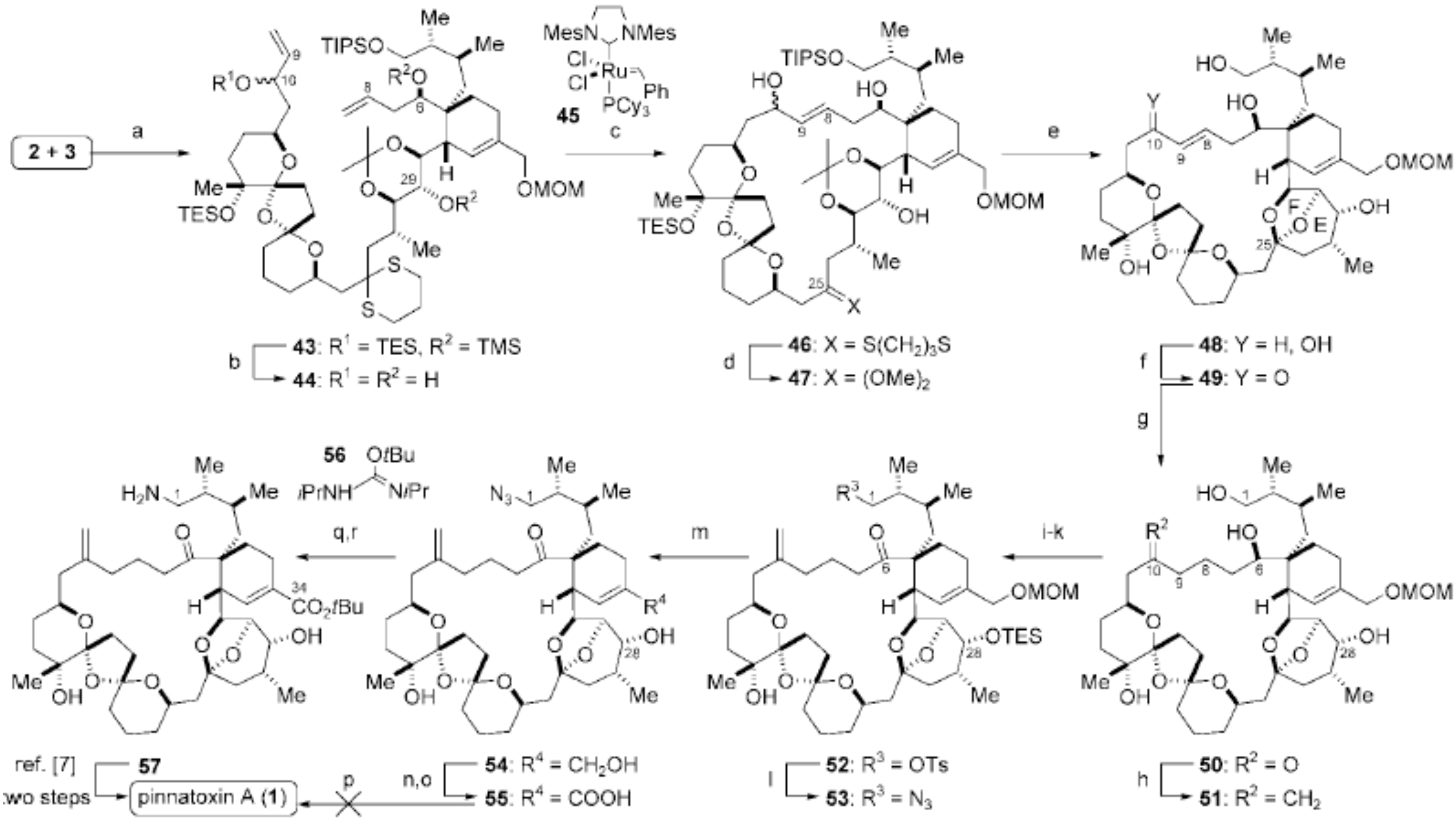
Synthesis of Pinnatoxin A - Hirama



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.

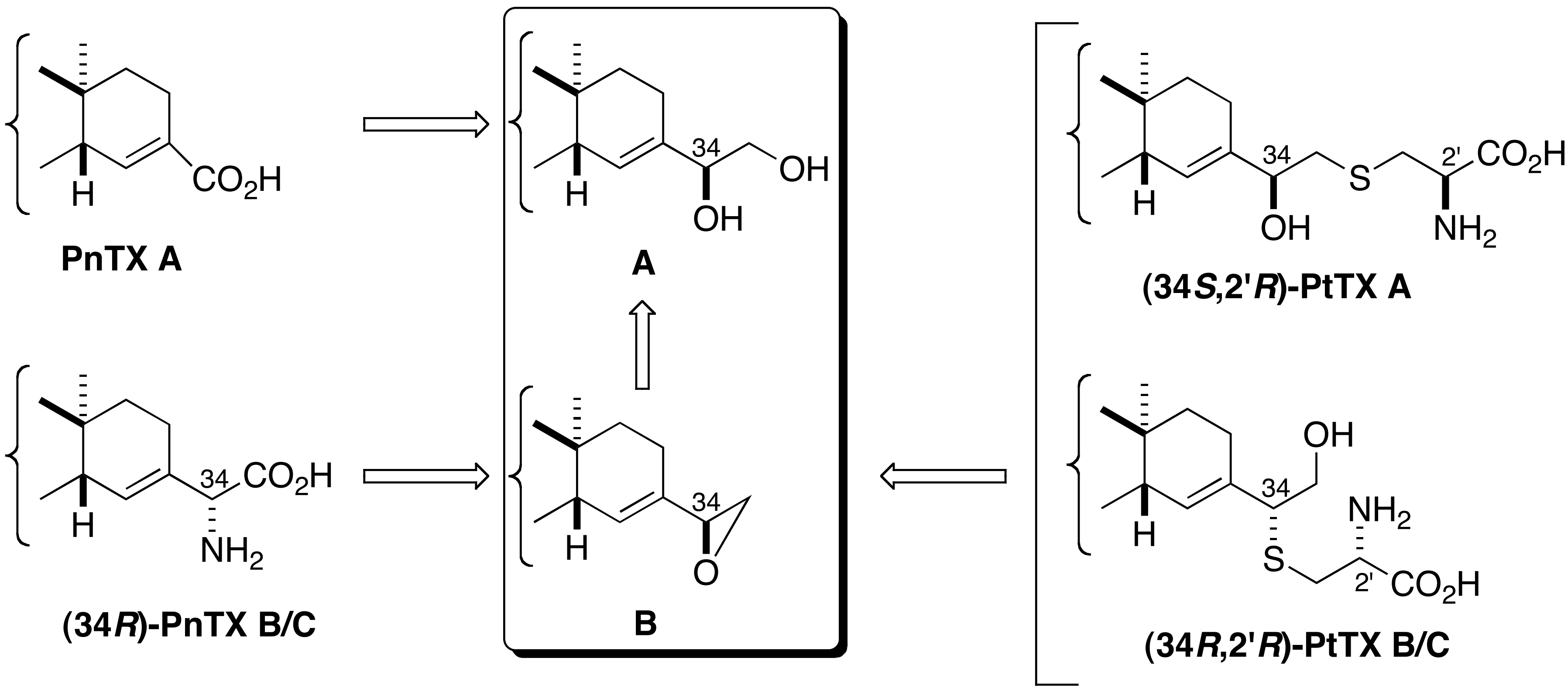
ACIE **2004**, *43*, 6505

Synthesis of Pinnatoxin A - Hirama



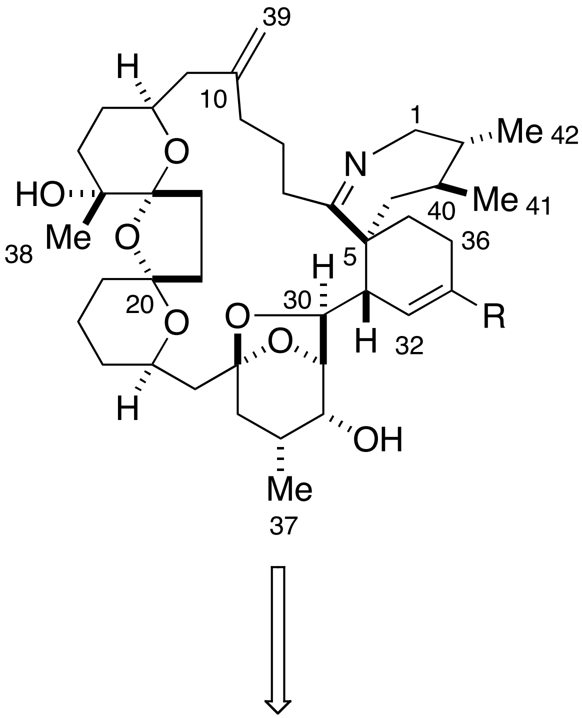
Scheme 5. Reagents and conditions: a) *t*BuLi (1.9 equiv), **2** (1.7 equiv), THF/HMPA (9:1), −78 °C, 95 % based on recovered **3** (41 %); b) TBAF, THF, 0 °C, 89 %; c) **45** (0.1 equiv), CH_2Cl_2, reflux, 75 %; d) $(CF_3CO_2)_2IPh$, molecular sieves (3 Å), $MeOH/CH_2Cl_2$ (20:9), room temperature; 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 %.

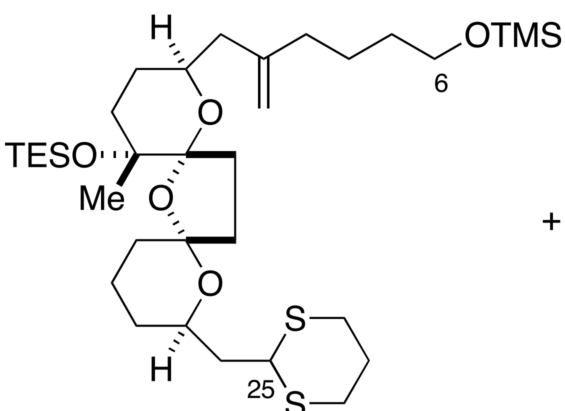
Unified Total Synthesis of the PnTX/PtTX Class of Marine Natural Products



JACS **2006**, *128*, 7463
OL ASAP

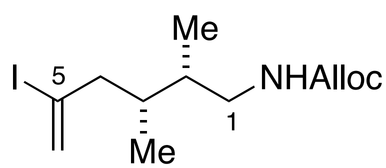
Retrosynthesis of Pinnatoxins and Pteriatoxins - Kishi





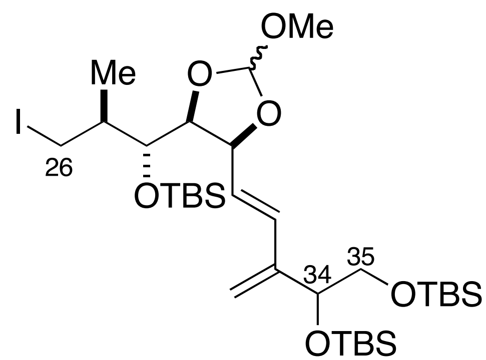
A

+



B

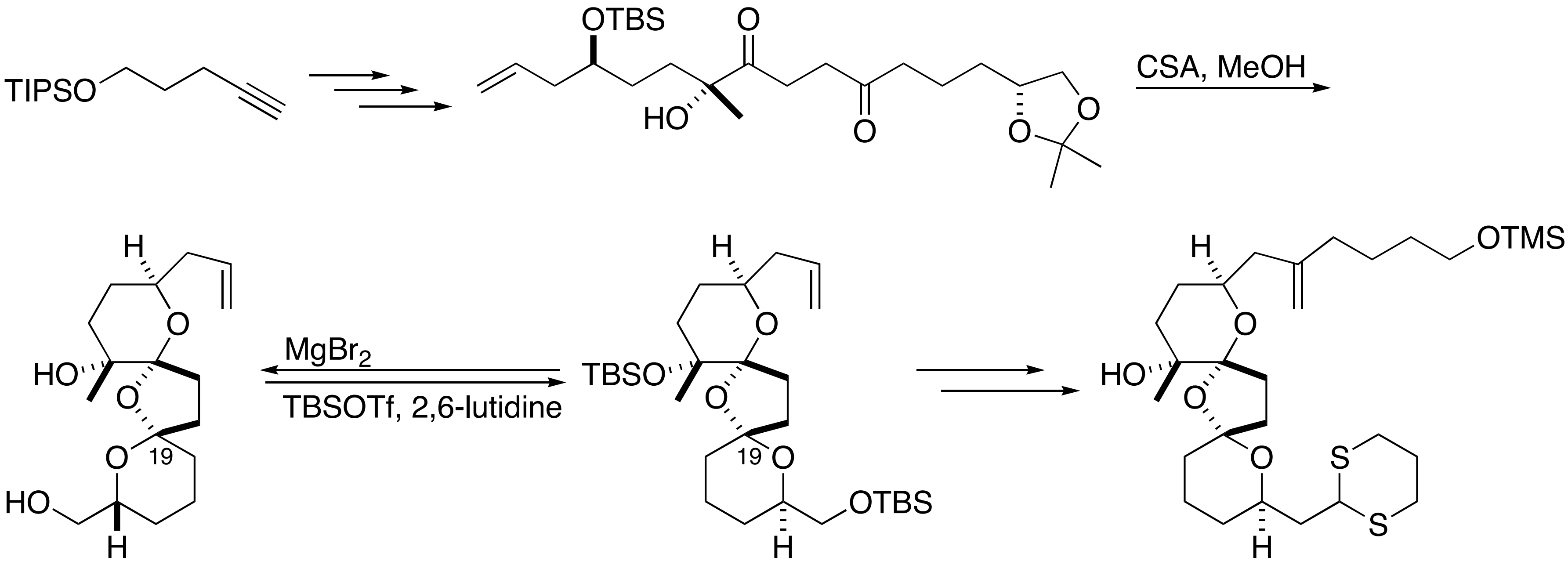
+



C

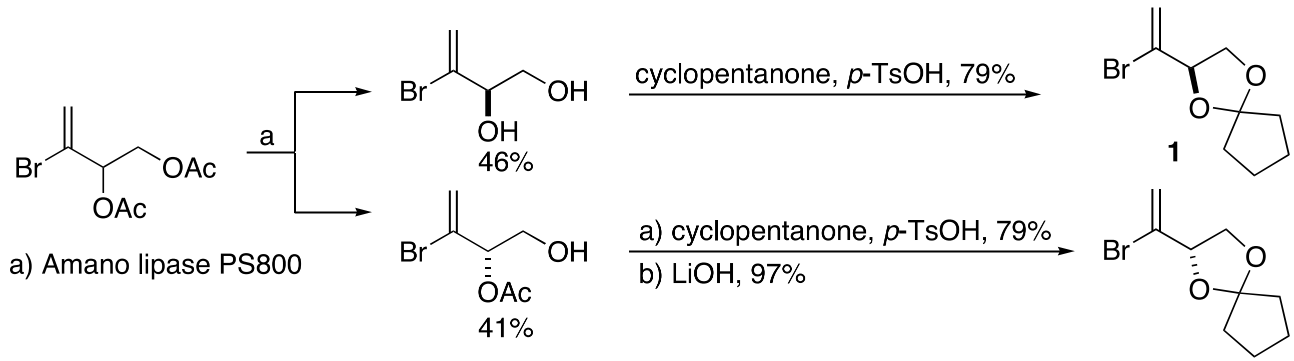
JACS **2006**, *128*, 7463

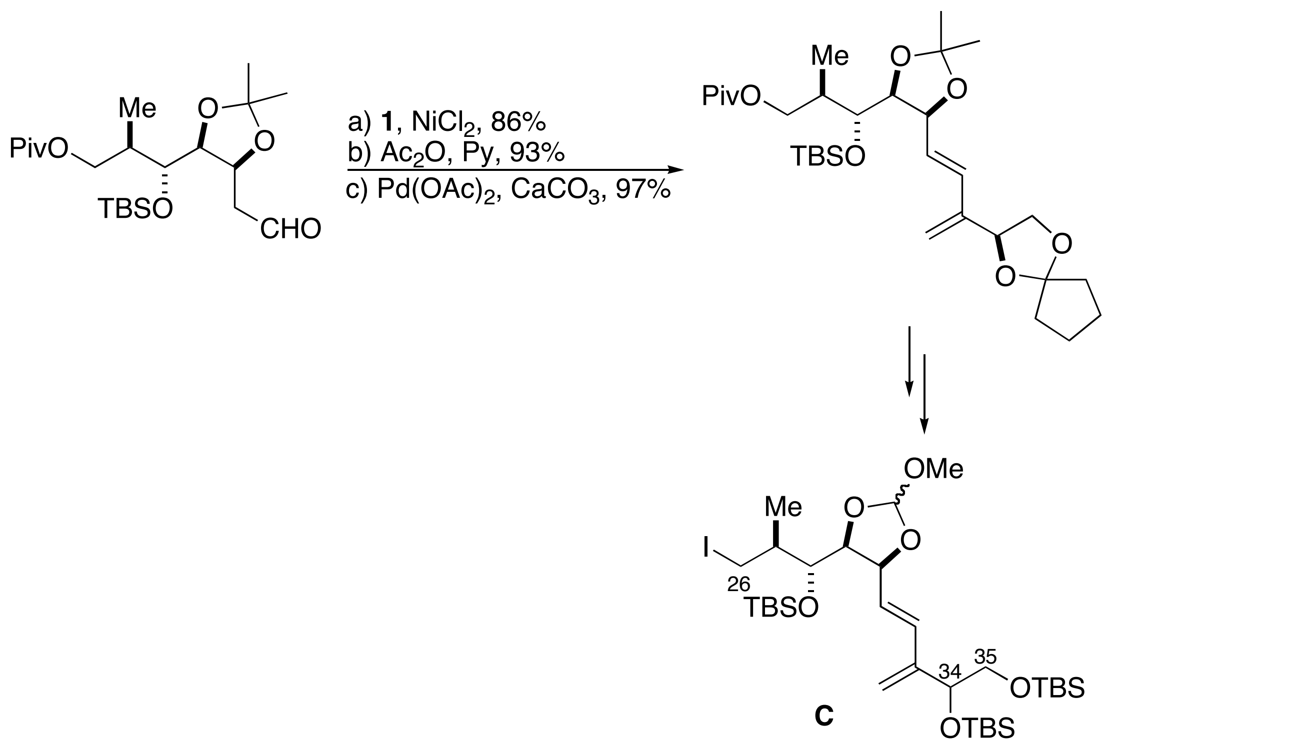
Synthesis of Fragment A



JACS **1998**, *120*, 7647

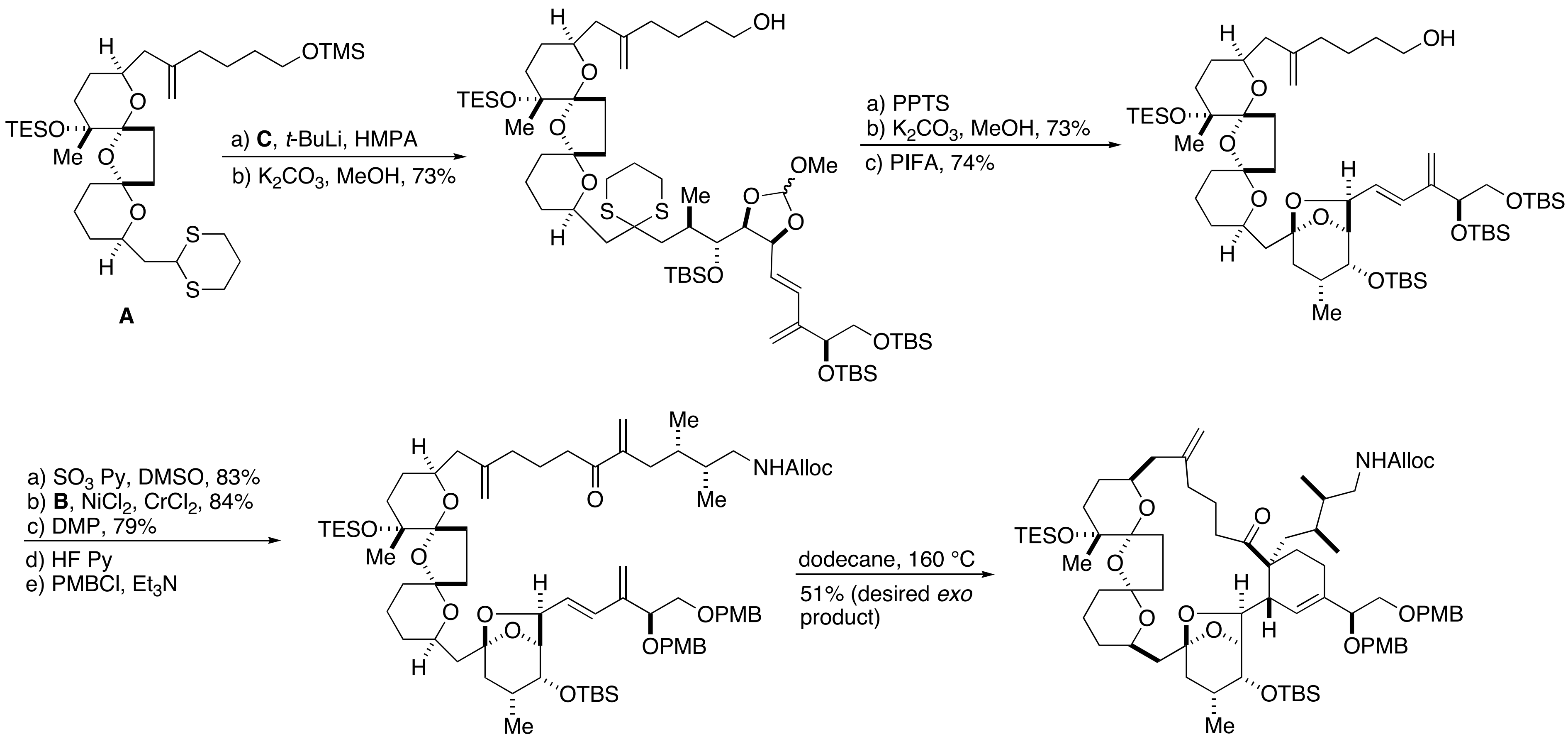
Synthesis of Fragment C





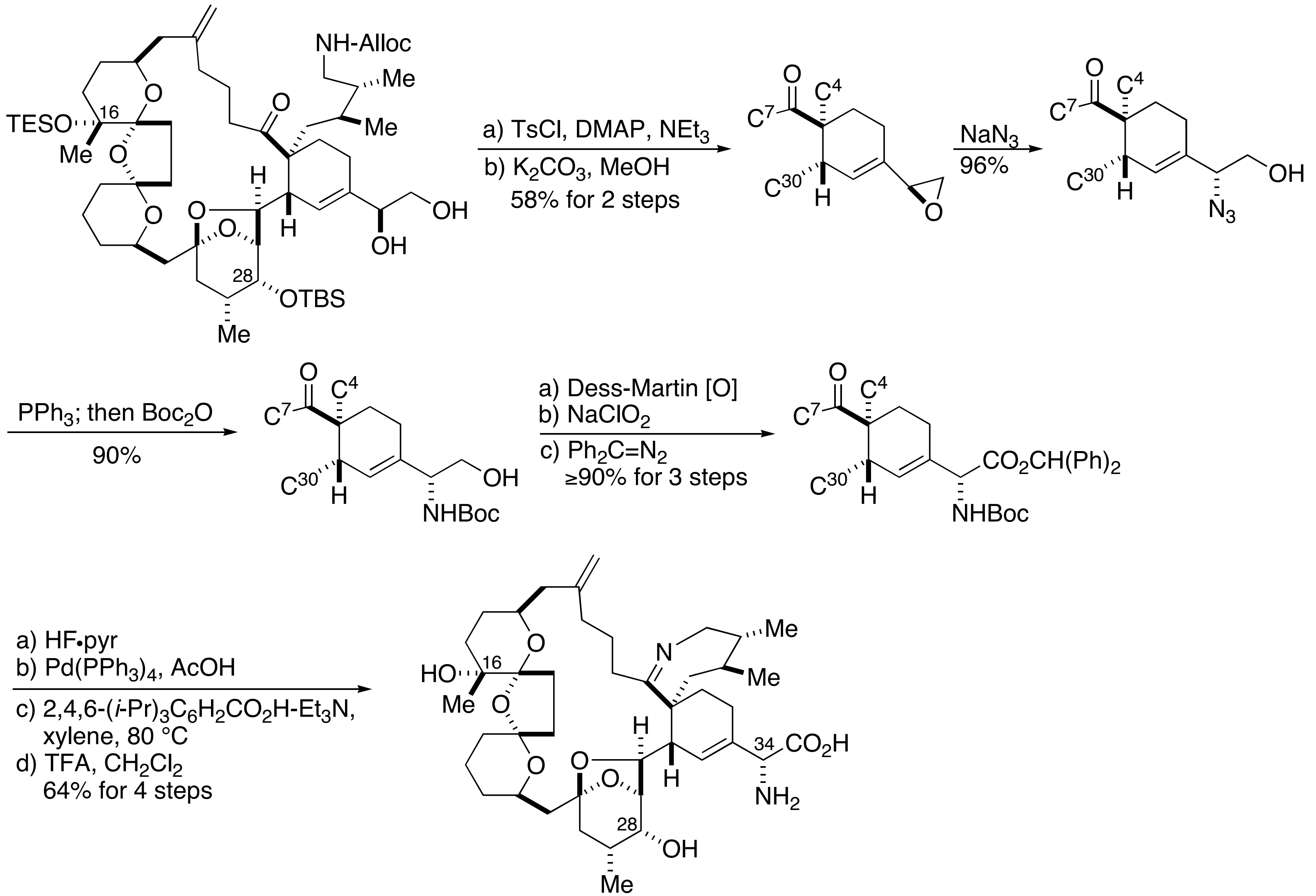
JACS **2006**, *128*, 7463

Synthesis of the Macrocycle



JACS **2006**, *128*, 7463

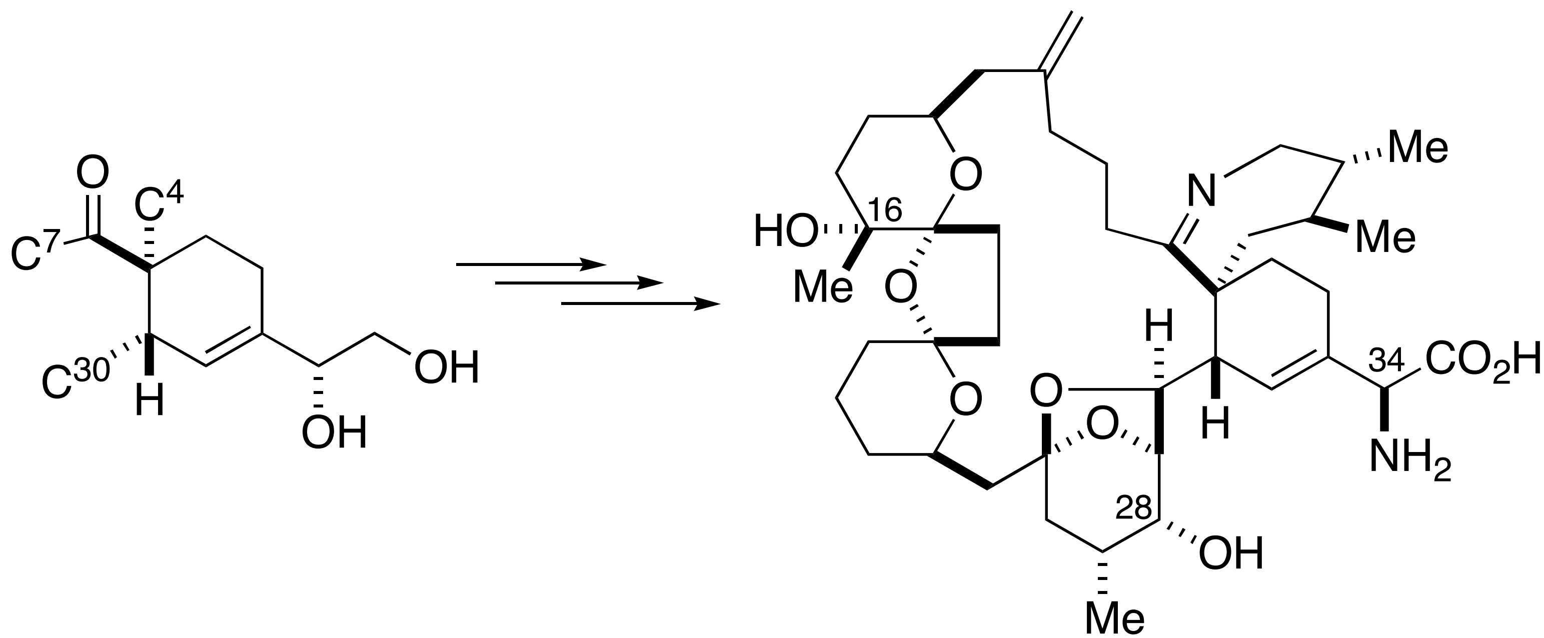
Total Synthesis of the Pinnatoxin C



PnTX C
(34*R*)-Diastereomer

OL ASAP

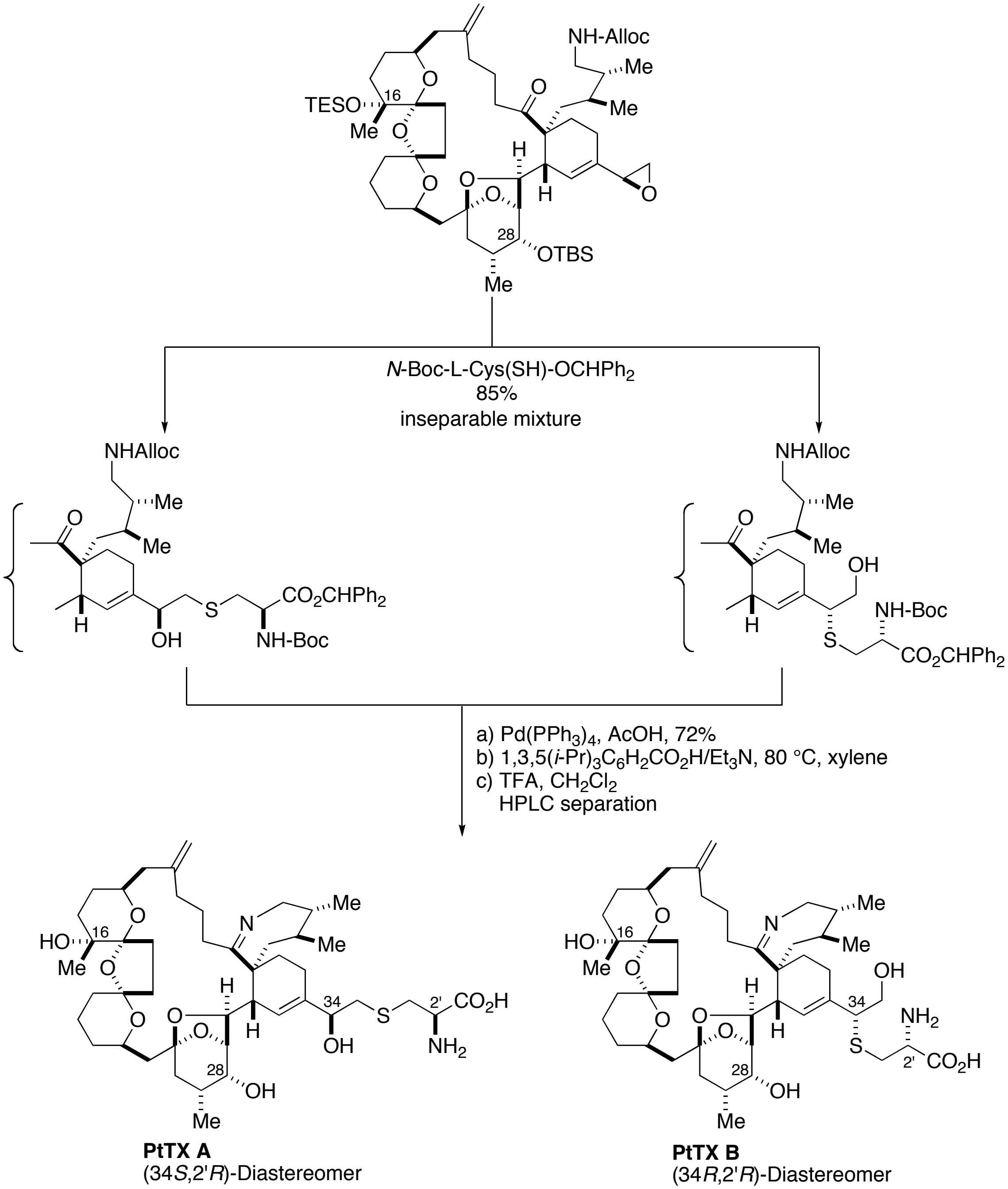
Total Synthesis of the Pinnatoxin B



PnTX B
(34*S*)-Diastereomer

OL ASAP

Total Synthesis of the Pteriatoxins A, B, and C



JACS **2006**, *128*, 7463

Summary

1) First Total Synthesis of PnTXs B and C in a Stereochemically Controlled Manner
Key Steps:
Intramolecular Diels Alder Reaction, Imine Cyclization, Nozaki-Hiyama-Kishi Reaction

2) Establishment of Stereochemistry at C34