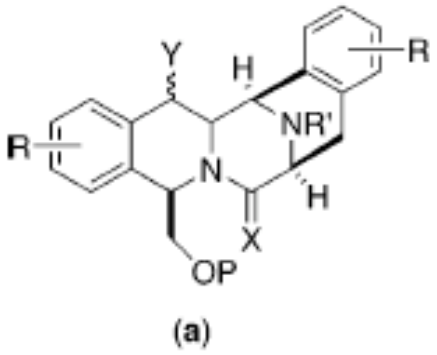
Total Synthesis of Cribrostatin

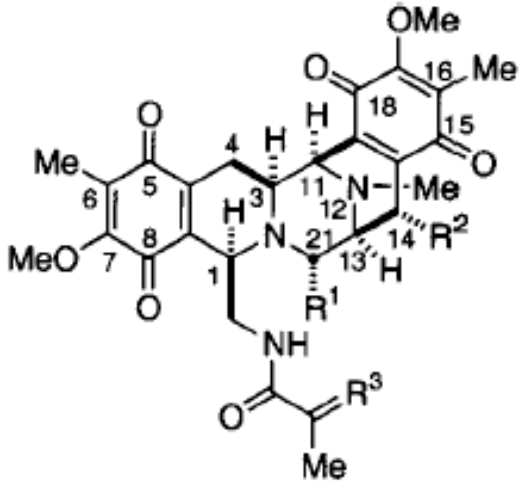
Chan, C.; Heid, R.; Zheng, S.; Guo, J.;
Zhou, B.; Furuuchi, T.; Danishefsky, S.J.,
*J.Am.Chem.Soc.***2005**, *127*, 4596

Tetrahydroisoquinoline Alkaloids

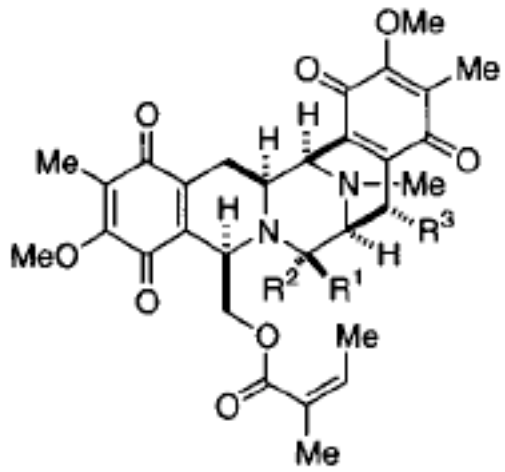


(a)

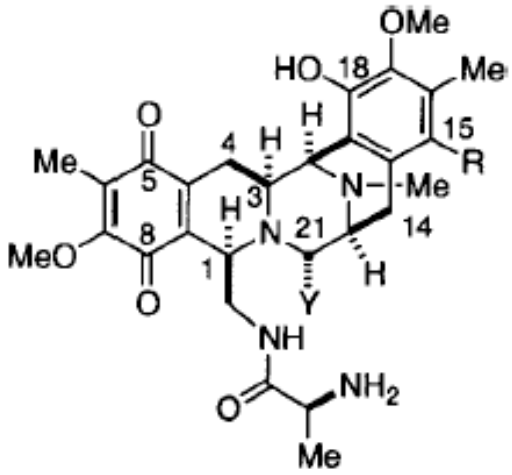
"Piperizinohydroisoquinoline Motif"



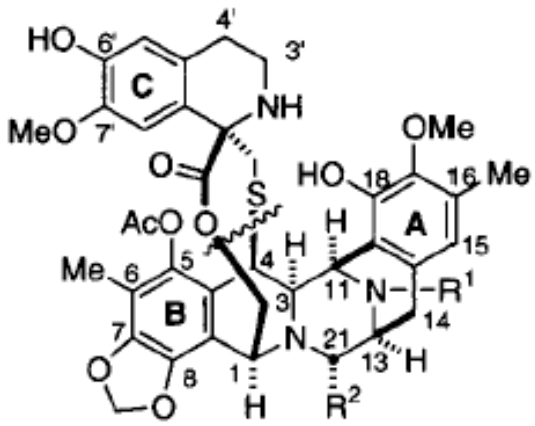
Saframycin A (**3**) R^1=CN, R^2=H, R^3=O



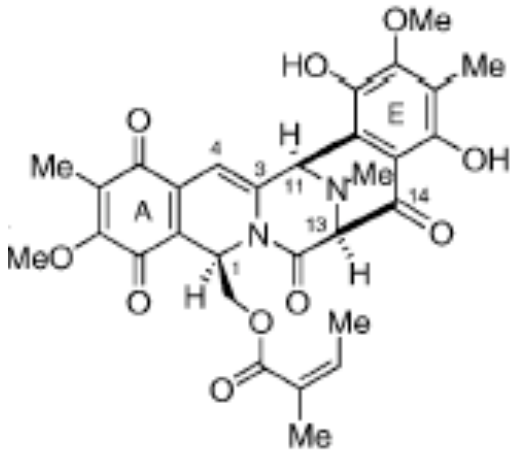
Renieramycin A (**138**) R^1=R^2=H, R^3=OH



safracin A (**159**) R=Y=H
B (**160**) R=H, Y=OH



Et 743 (**170**) R^1=Me, R^2=OH



Cribrostatin IV (1)

Williams, R.M.; Scott, J.D., *Chem.Rev.***2002**, *102*, 1639

Some Facts About Et-743

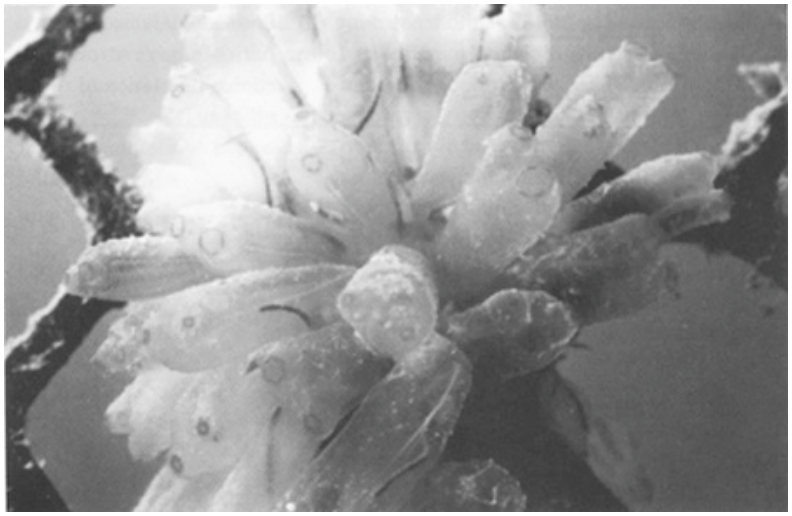
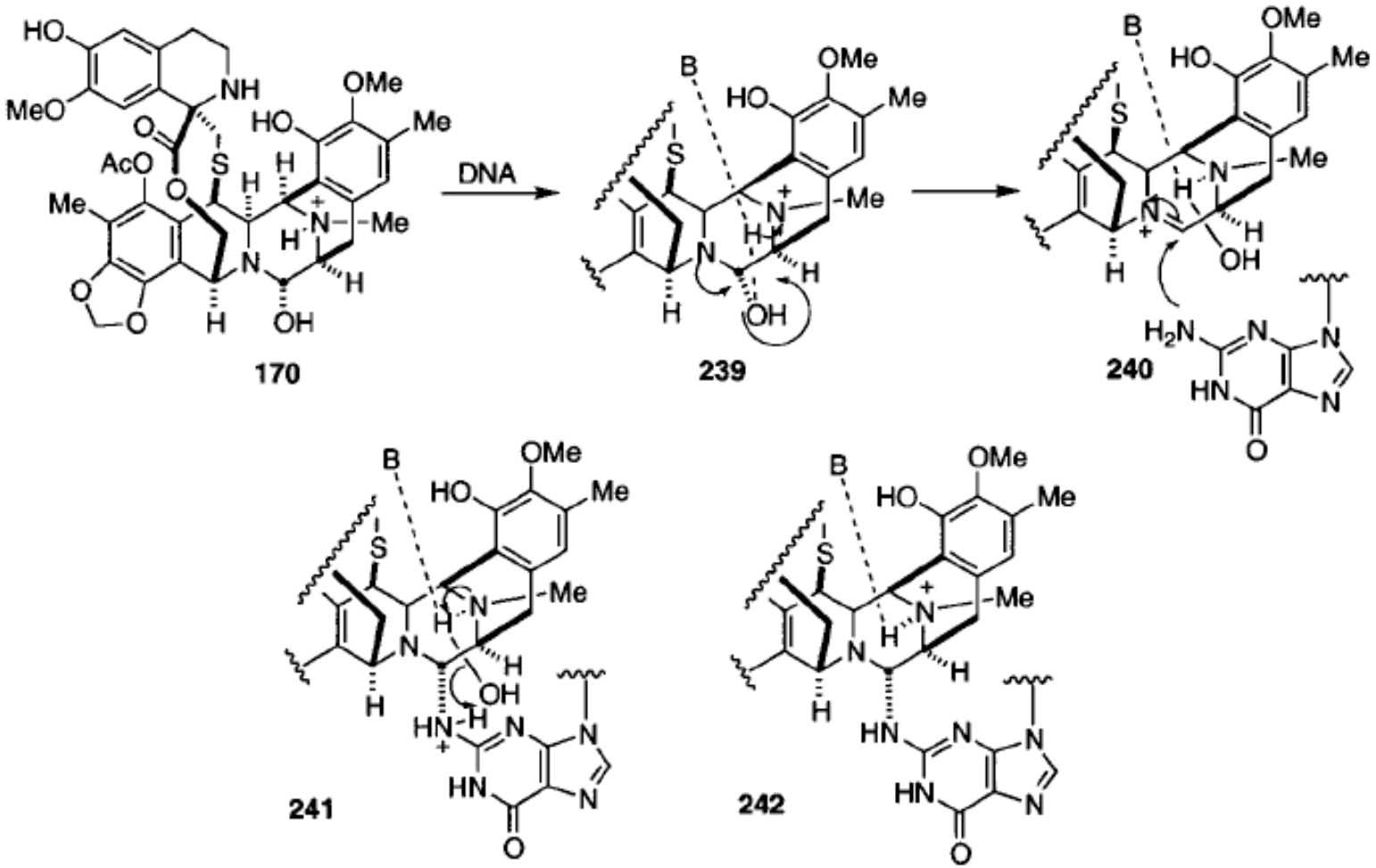


Table 4. Activity of Et 743 against Several Tumor Cell Lines

tumor type	IC_{50} (μM)
P388 leukemia	0.00034
L1210 leukemia	0.00066
A549 lung cancer	0.00026
HT29 colon cancer	0.00046
MEL-28 melanoma	0.00050

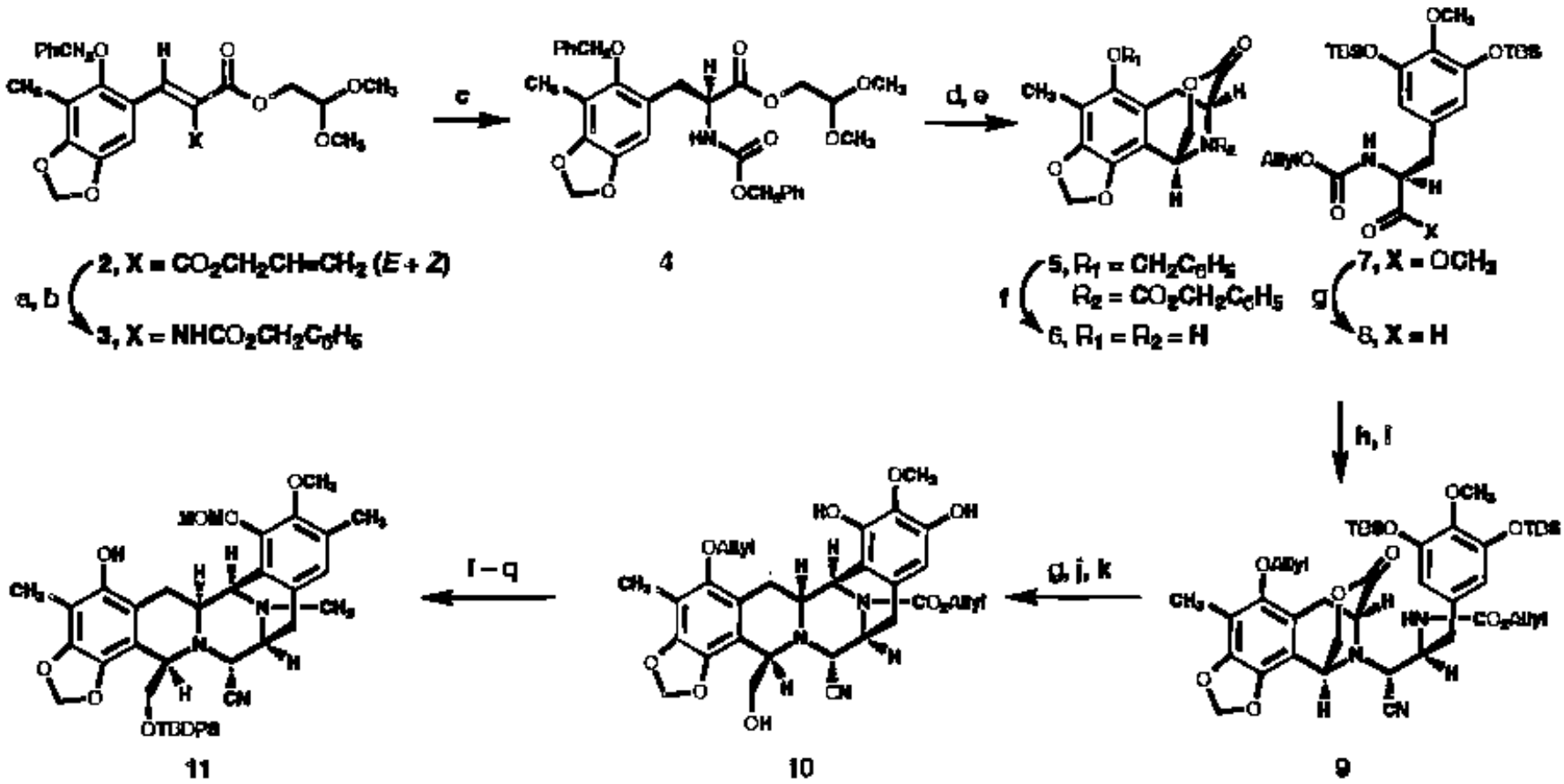
- Isolated by Rinehart in 1990 from tunicate Ecteinascidia turbinata sea squirts in Carribean and Mediterrenean seas
- Sea squirts currently produced in bulk quantities in underwater farms By Pharma Mar company
- 95,000 pounds of sea squirts afford only 3 ounces of the active drug
- Active against connective tissue, breast, ovary and prostate tumors

Proposed Pathway of Biological Action



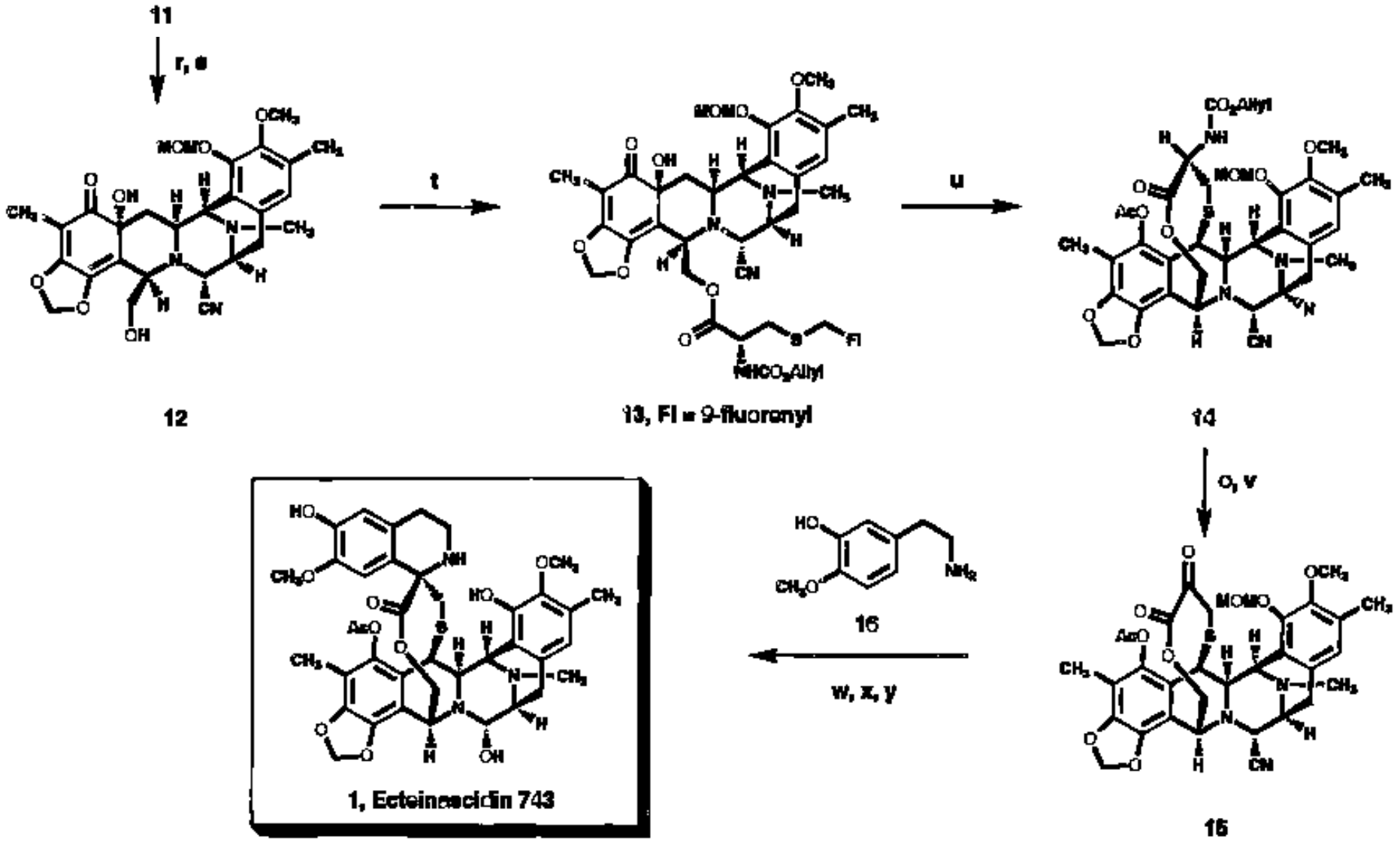
Williams, R.M.; Scott, J.D., *Chem.Rev.***2002**, *102*, 1639

Corey's Convergent Approach to Et-743



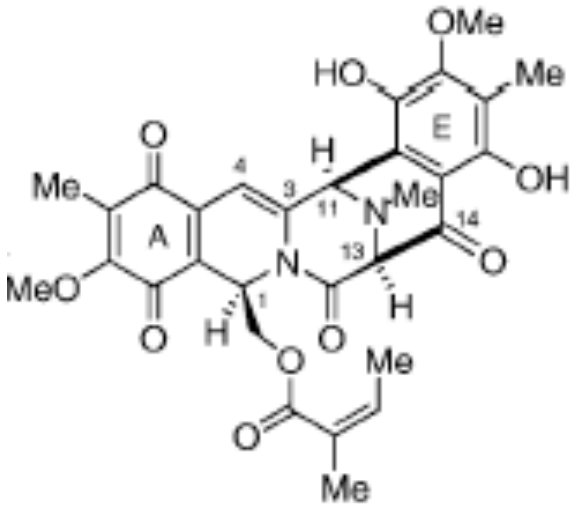
[a] Reagents: (a) Et_3N-HCO_2H, $Pd(PPh_3)_4$; (b) $(PhO)_2P(O)N_3$, Et_3N, 4 Å molecular sieves; 70 °C, BnOH; (c) Rh[(COD))-(*R*,*R*)-DiPAMP]$^+BF_4^-$, 3 atm of H_2; (d) $BF_3{\cdot}OEt_2$, H_2O; (e) $BF_3{\cdot}OEt_2$, 4 Å molecular sieves; (f) 10% Pd/C, H_2; (g) DIBAL, −78 °C; (h) HOAc, KCN; (i) allyl bromide, Cs_2CO_3; (j) $KF{\cdot}2H_2O$; (k) CH_3SO_3H, 3 Å molecular sieves; (l) Tf_2NPh, Et_3N, DMAP; (m) TBDPSCl, DMAP; (n) MOMBr, *i*-Pr_2NEt; (o) $PdCl_2(PPh_3)_2$, Bu_3SnH, HOAc; (p) CH_2O, $NaBH_3CN$, HOAc; (q) $PdCl_2(PPh_3)_2$, $SnMe_4$, LiCl, 80 °C;

Completion of Synthesis

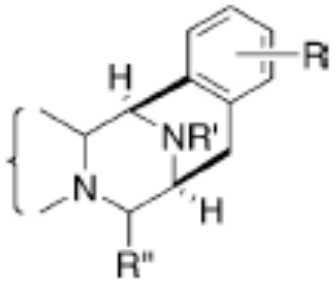


(r) $(PhSeO)_2O$; (s) TBAF; (t) Alloc-Cys(CH_2Fl)-OH, EDC·HCl, DMAP; (u) DMSO, Tf_2O, −40 °C; *i*-Pr_2NEt, 0 °C; *t*-BuOH, 0 °C; $(Me_2N)_2C{=}N$-*t*-Bu, 23 °C; Ac_2O, 23 °C; (v) [*N*-methylpyridinium-4-carboxaldehyde]$^+I^-$, DBU, $(CO_2H)_2$; (w) **16**, silica gel; (x) CF_3CO_2H, H_2O; (y) $AgNO_3$, H_2O.

Cribrostatin IV - Structural Features and Biological Activity



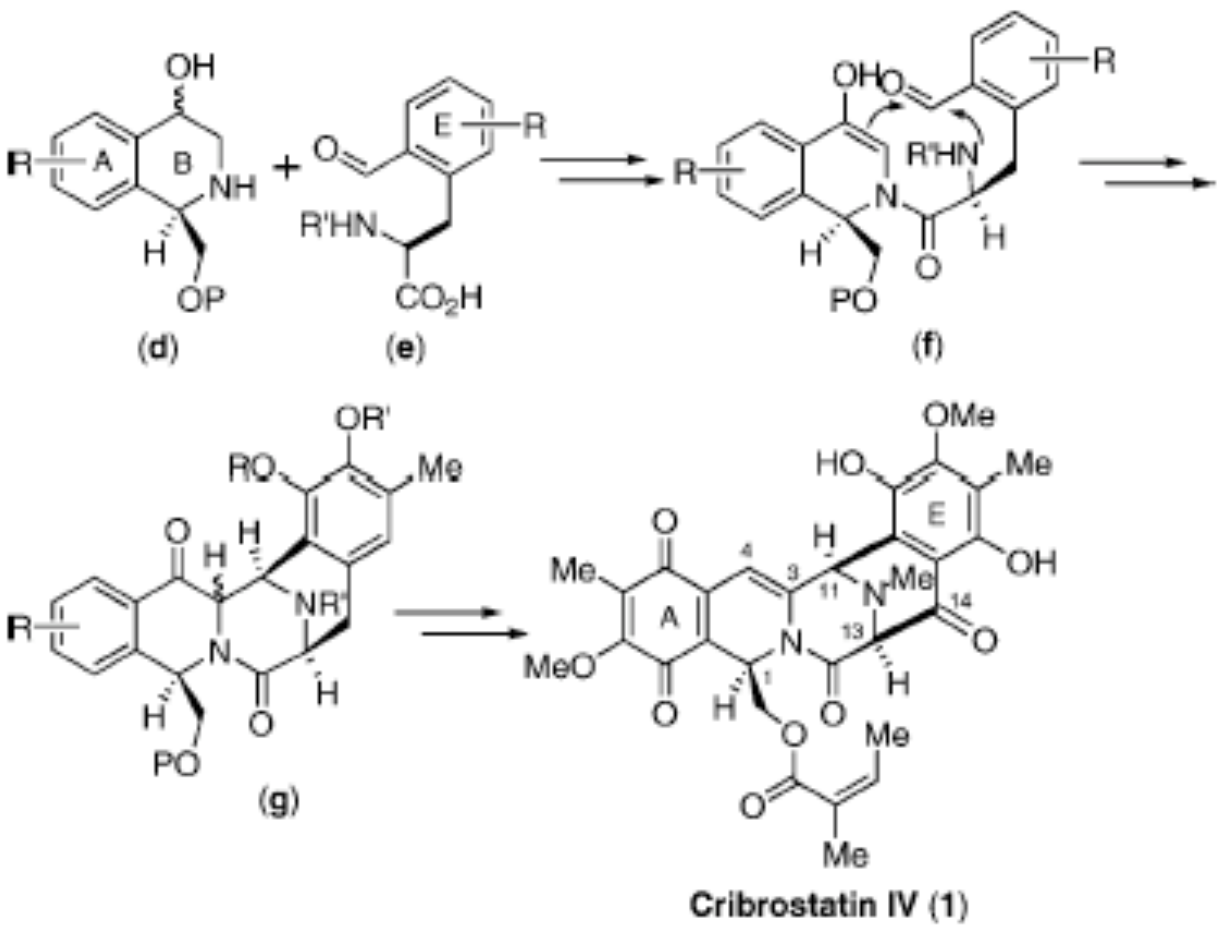
Cribrostatin IV (1)



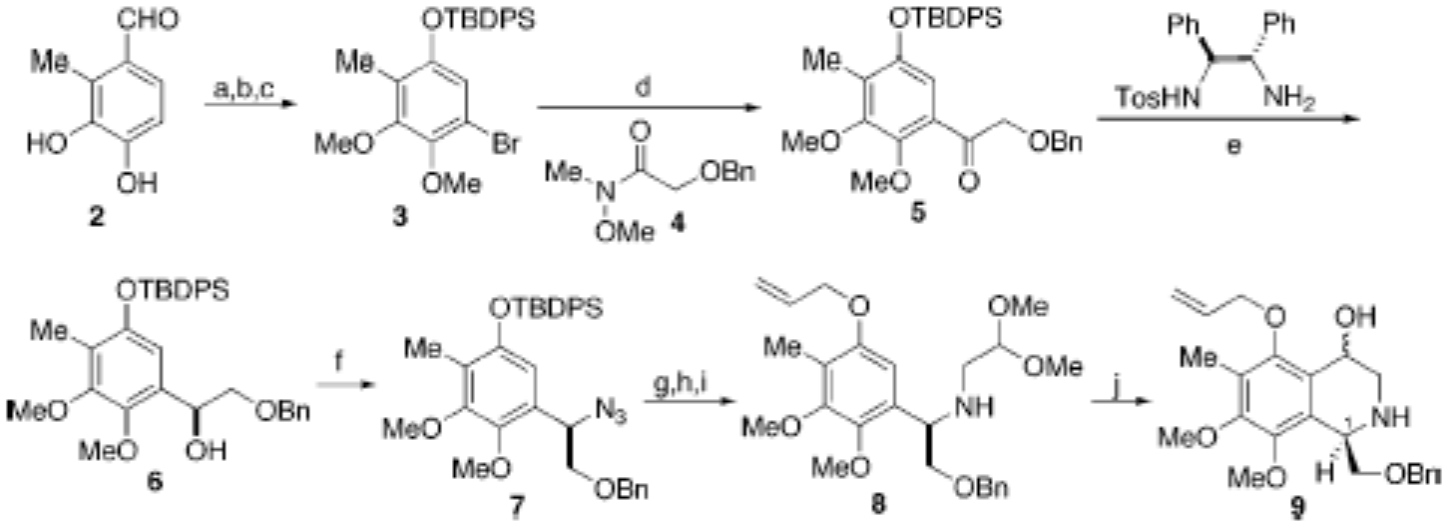
(c) R"=-CN, -OH

- Isolated by Petit in **2000** from blue marine sponge, Cribrochalina in the reef passages in the Republic of Maldives
- Highly functionalized of pentacyclic alkaloids with every skeletal carbon in highly oxidized form
- Extremely potent (Low micromolar) cytotoxic agent

Synthetic Strategy for Cribrostatin

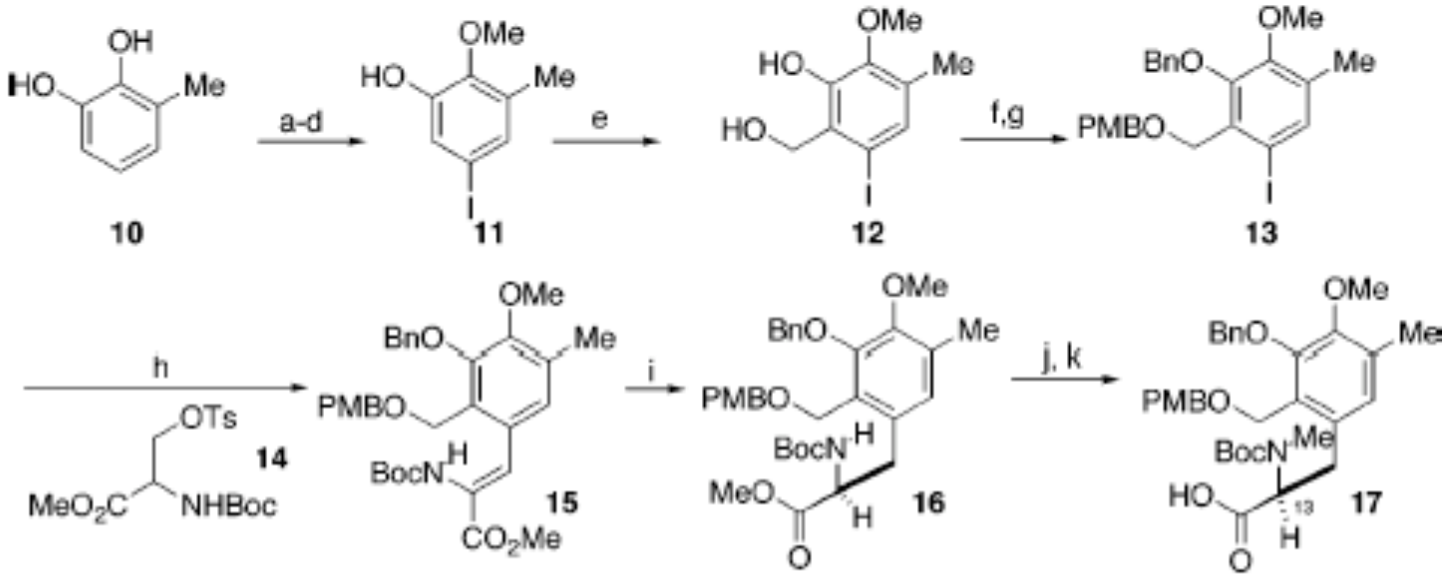


Synthesis of Coupling Partner **9**



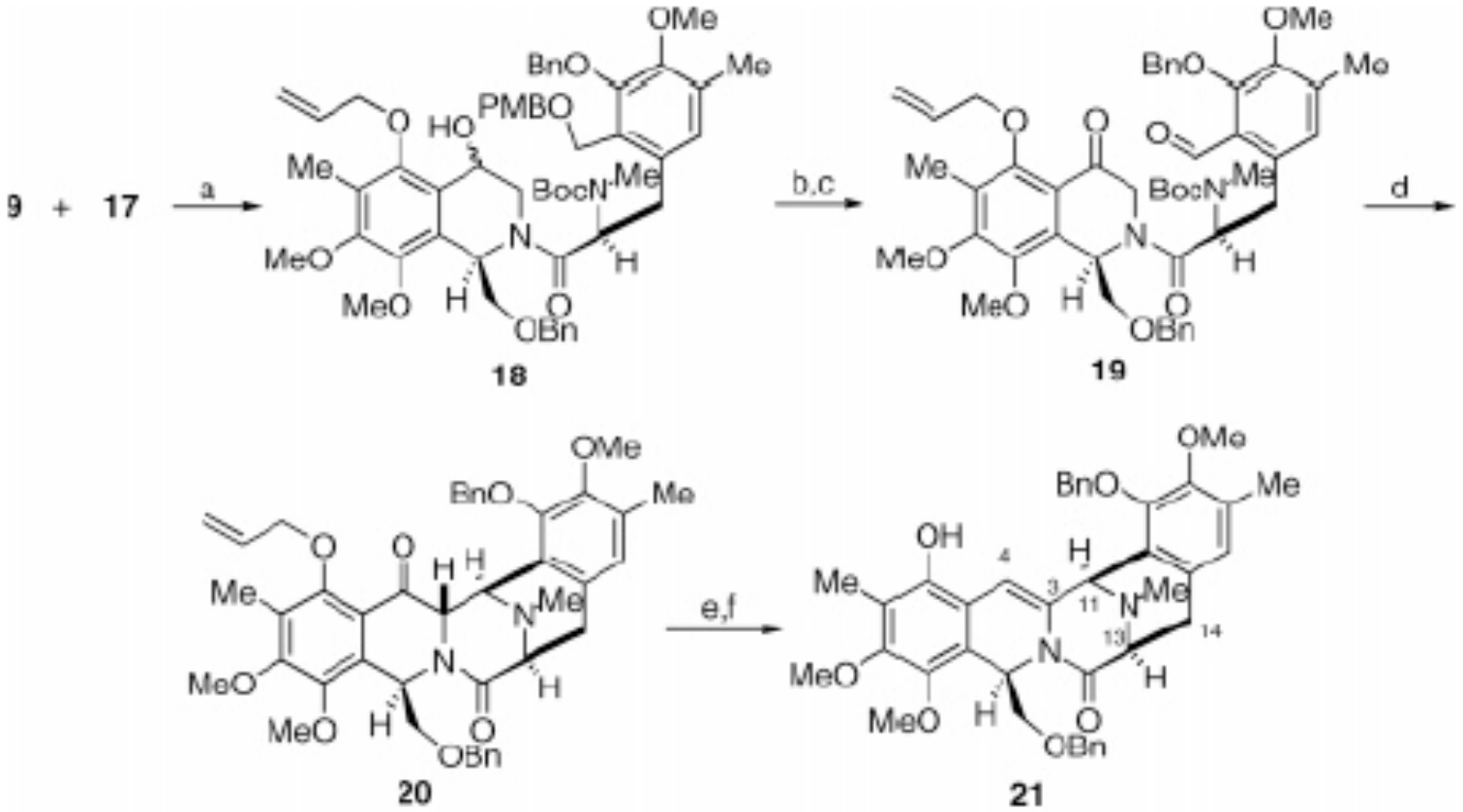
[a] Key: (a) i. Br_2, NaOAc, AcOH; ii. Me_2SO_4, Bu_4NBr, NaOH, CH_2Cl_2, 76% over two steps; (b) i. mCPBA, $CHCl_3$; ii. HCl, MeOH, 78% over two steps; (c) TBDPSCl, TEA, DMAP, DMF, 89%; (d) i. *n*-BuLi, toluene:THF (9:1), −78 °C; ii. **4**, 80% over two steps; (e) $(RuCl_2)_2$(*p*-cymene)$_2$, DMF/HCO_2H/TEA, 40 °C, 94%, 95% ee; (f) DPPA, DBU, toluene:DMF (9:1), 50 °C, 82%, 95% ee; (g) 5% Pd/C, 1 atm H_2, EtOAc, 80%; (h) i. $(MeO)_2CHCHO$, AcOH, $NaCNBH_3$, $MgSO_4$, MeOH; ii. TBAF, THF, 99% over two steps; (i) allyl bromide, NaH, DMF, 87%; (j) 8.0 M HCl/dioxane, 97%.

Synthesis of Coupling Partner **17**



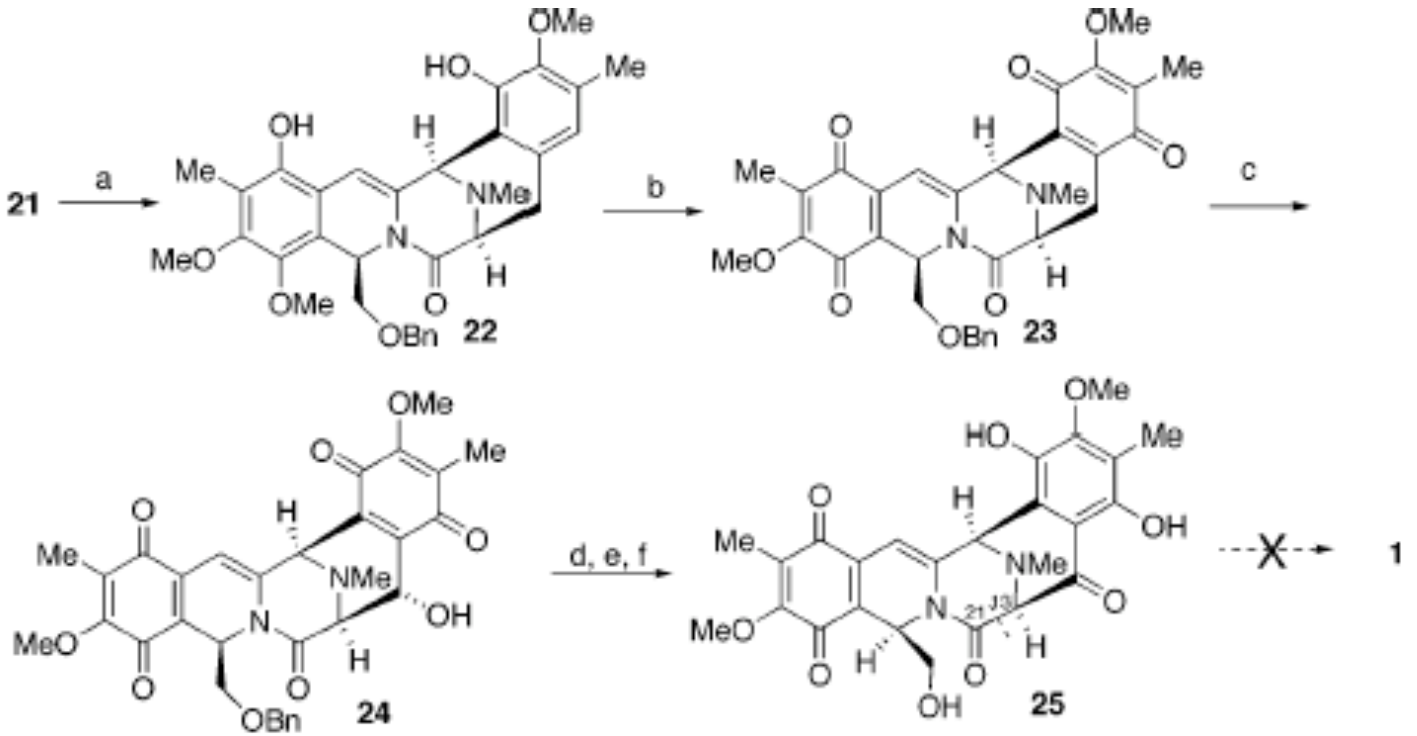
[a] Key: (a) TsCl, Et_3N, CH_2Cl_2, 84%; (b) ICl, AcOH, 96%; (c) MeI, K_2CO_3, acetone, 95%; (d) NaOH, EtOH, 90%; (e) $(CH_2O)_n$, Et_2AlCl, CH_2Cl_2, 86%; (f) BnBr, K_2CO_3, acetone, 85%; (g) PMBCl, NaH, THF:DMF, 99%; (h) TEA, **14**,[18] Bu_4NBr, (*o*-tolyl)$_3$P, $Pd(OAc)_2$, CH_3CN, 87% (Z isomer only); (i) Rh[(COD)-(*S*,*S*)-Et-DuPhos]$^+TfO^-$, 100 psi H_2, CH_2Cl_2/MeOH, 93%, 99% ee; (j) LiOH, MeOH/THF/H_2O, 93%; (k) MeI, NaH, THF, 82%.

Cyclization Leading to Pentacyclic core 21



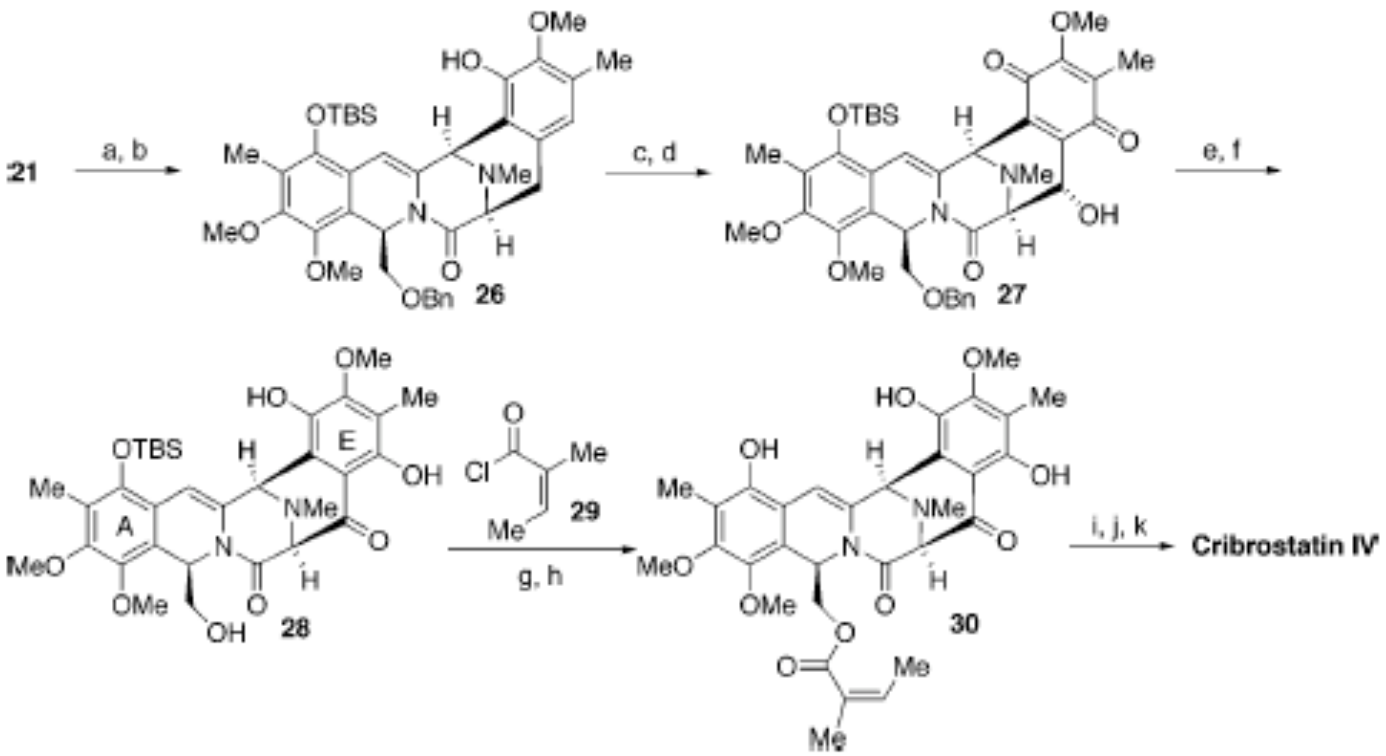
[a] Key: (a) BOPCl, TEA, CH_2Cl_2, 89%; (b) DDQ, CH_2Cl_2/buffer (pH 7), 90%; (c) DMP, 2,6-lutidine, CH_2Cl_2, 84%; (d) HCO_2H, 100 °C, 59%; (e) i. $NaBH_4$, THF/H_2O; ii. AcOH, Bu_3SnH, $(Ph_3P)_2PdCl_2$, CH_2Cl_2,[3] 98% over two steps; (f) CSA, benzene, 80 °C, 80%.

Unsuccessful Route Towards 1



[a] Key: (a) 5% Pd/C, H_2 (1 atm) EtOAc; (b) Fremy salt, KH_2PO_4, CH_3CN/H_2O; (c) SeO_2, dioxane, 100 °C; (d) DMP, CH_2Cl_2; (e) 10% Pd/C, H_2 (1 atm), MeOH; (f) air, MeOH.

Completion of Synthesis



[a] Key: (a) TBSOTf, TEA, CH_2Cl_2, 90%; (b) 5% Pd/C, H_2 (1 atm), EtOAc, 90%; (c) Fremy salt, KH_2PO_4, CH_3CN/H_2O, 84%; (d) SeO_2, dioxane, 100 °C, 87%; (e) DMP, CH_2Cl_2; (f) 10% Pd/C, H_2 (1 atm), MeOH, 89% over two steps; (g) **29**, CH_2Cl_2; (h) AcOH, TBAF, THF, 75% over two steps; (i) PIFA, CH_3CN/H_2O; (j) Zn, AcOH; (k) air, DMF, 24 h, 65% over three steps.