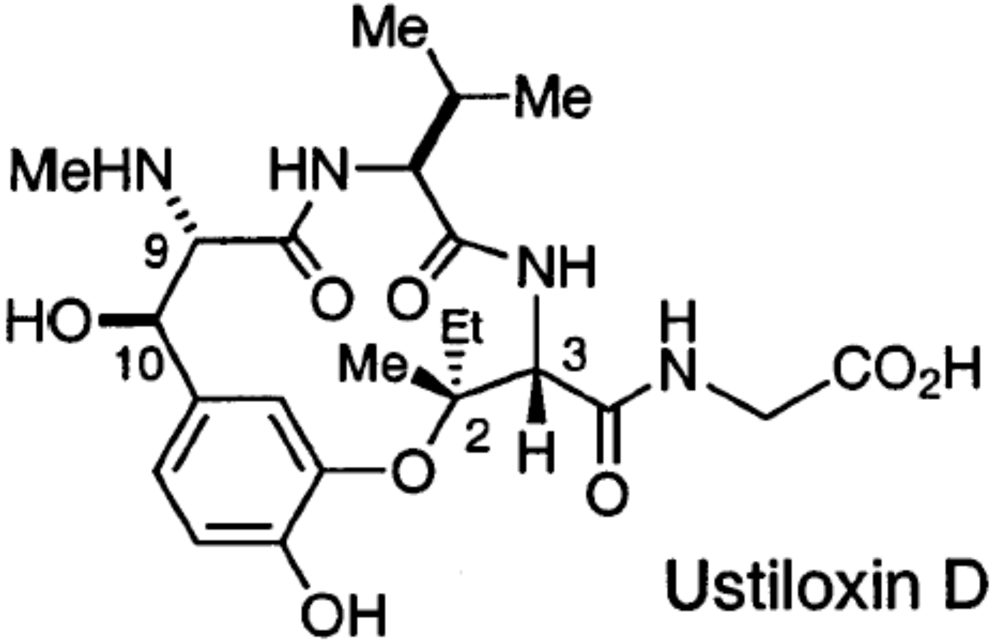
Total Syntheses of Ustiloxin D



Ustiloxin D

Joullie, M. M; Evans, C. D; Li, P. *Org Lett,* **2005**, 23, 5325.

Wandless, T. J; Sawayama, A. M; Tanaka, H. *J. Am. Chem. Soc,* **2003**, 125, 6864.

Joullie, M. M; Evans, C. D; Li, P. *J. Am. Chem. Soc,* **2002**, 124, 520.

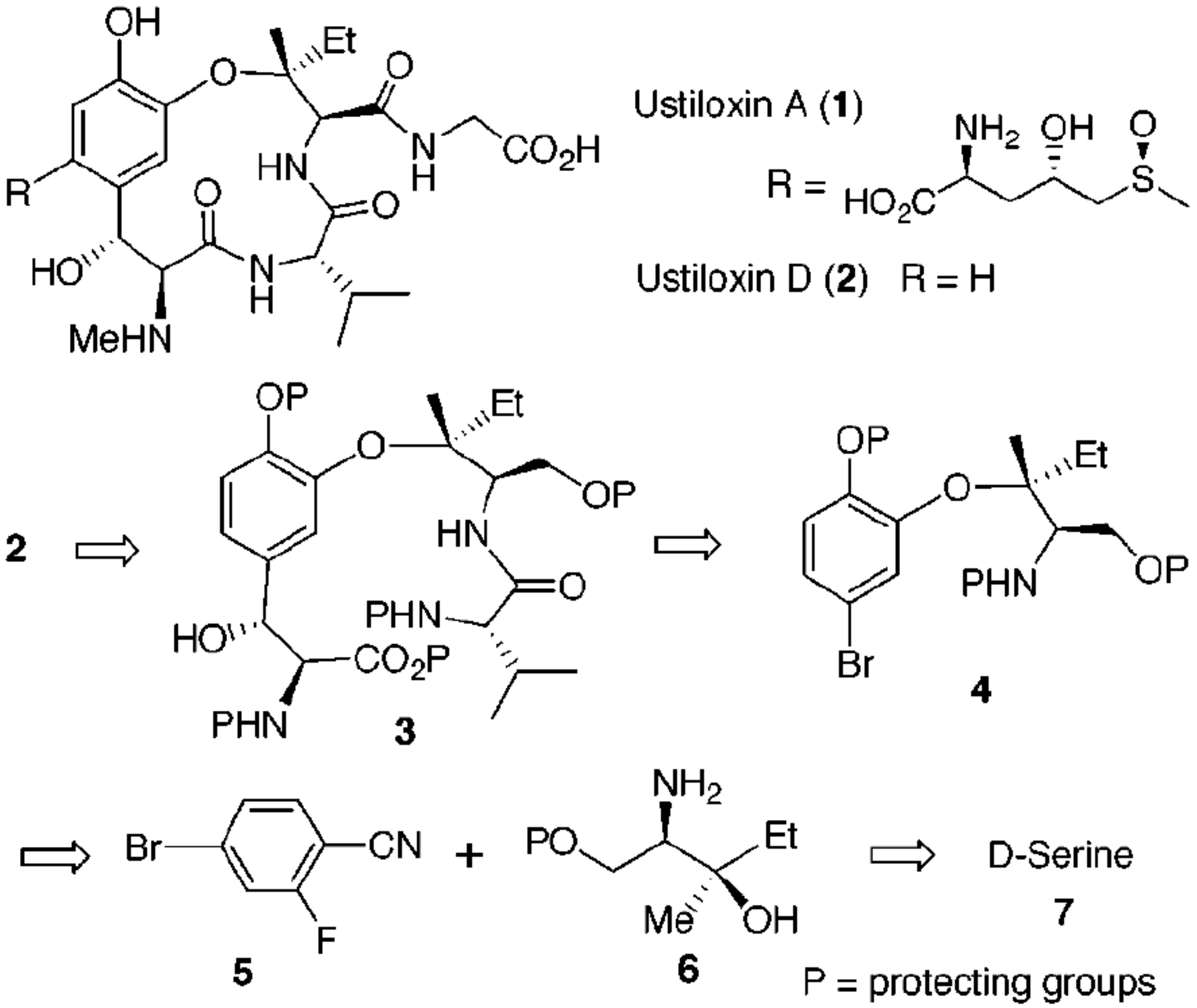
False Smut


Figure 2

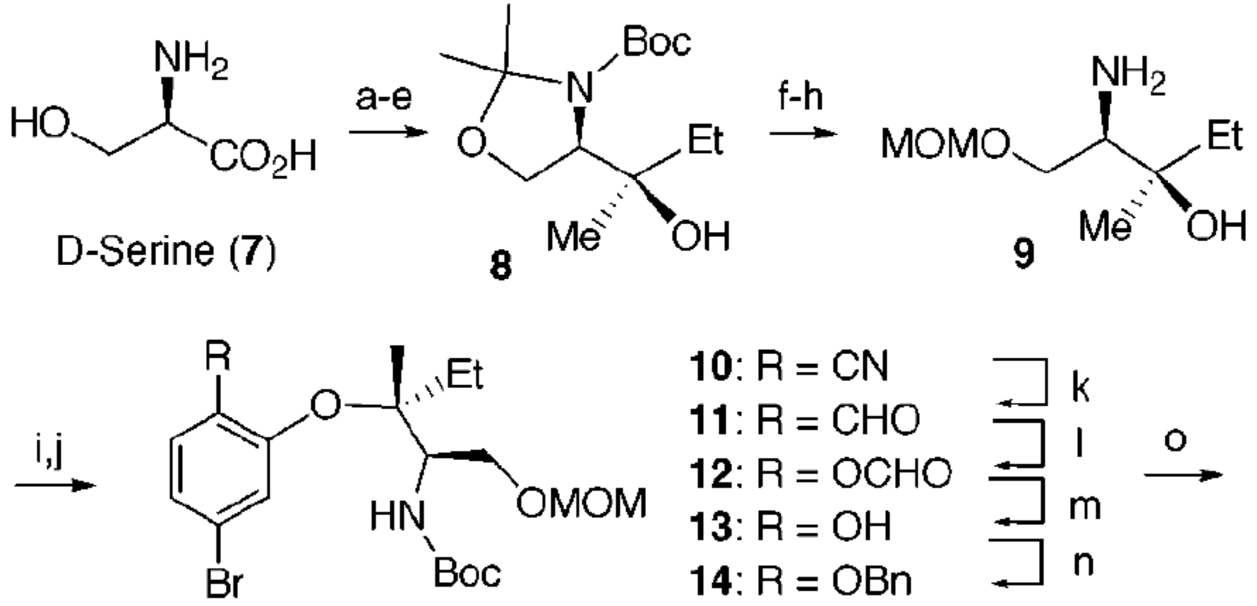

Figure 1


Figure 3

Joullie's First Retrosynthetic Analysis of Ustiloxin D

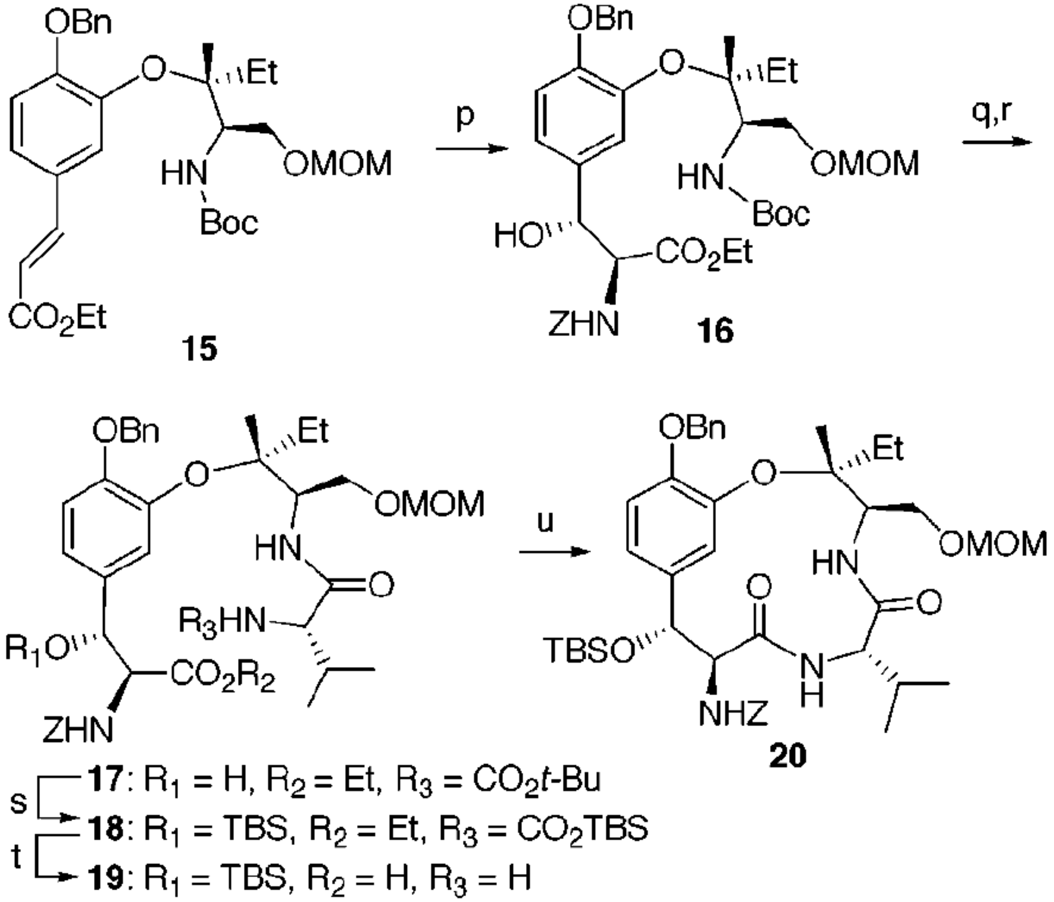


Joullie’s First Generation Synthetic Approach



[a] Key: (a) Boc_2O, $NaHCO_3$, dioxane−H_2O; (b) MeNH(OMe)·HCl, EDCI·HCl, THF−H_2O, pH 4.5, 4 h, 71% for 2 steps; (c) $(MeO)_2CMe_2$, catalytic *p*-TsOH, 97%; (d) MeLi, THF, −78 to −65 °C, 72%; (e) EtMgBr, THF, −78 to −20 °C, ds = 9:1, 58%; (f) *p*-TsOH, MeOH; (g) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, 0 °C to room temperature, 71% for 2 steps; (h) TFA, CH_2Cl_2, 0 °C, 78%; (i) 4-bromo-2-fluorobenzonitrile (**5**), 1.1 equiv of KHMDS, THF, 0 °C to room temperature, 78%; (j) Boc_2O, Et_3N, CH_2Cl_2, 81%; (k) Raney nickel, NaH_2PO_2, Pyr:H_2O:HOAc (2:1:1), 0−55 °C, 56%; (l) 30% H_2O_2, 4 mol % bis(2-nitrophenyl)diselenide, CH_2Cl_2, room temperature, 24 h; (m) KOH, MeOH−H_2O, 73% for 2 steps; (n) BnBr, K_2CO_3, *n*-Bu_4NI, DMF, 96%; (o) ethyl acrylate, $Pd(OAc)_2$, $(o\text{-tolyl})_3P$, Et_3N, CH_3CN, reflux, 6 h, 95%; (p) NaOH, $BnOCONH_2$, *t*-BuOCl, $K_2[OsO_2(OH)_4]$,

Joullie's First Generation Synthetic Approach Continued



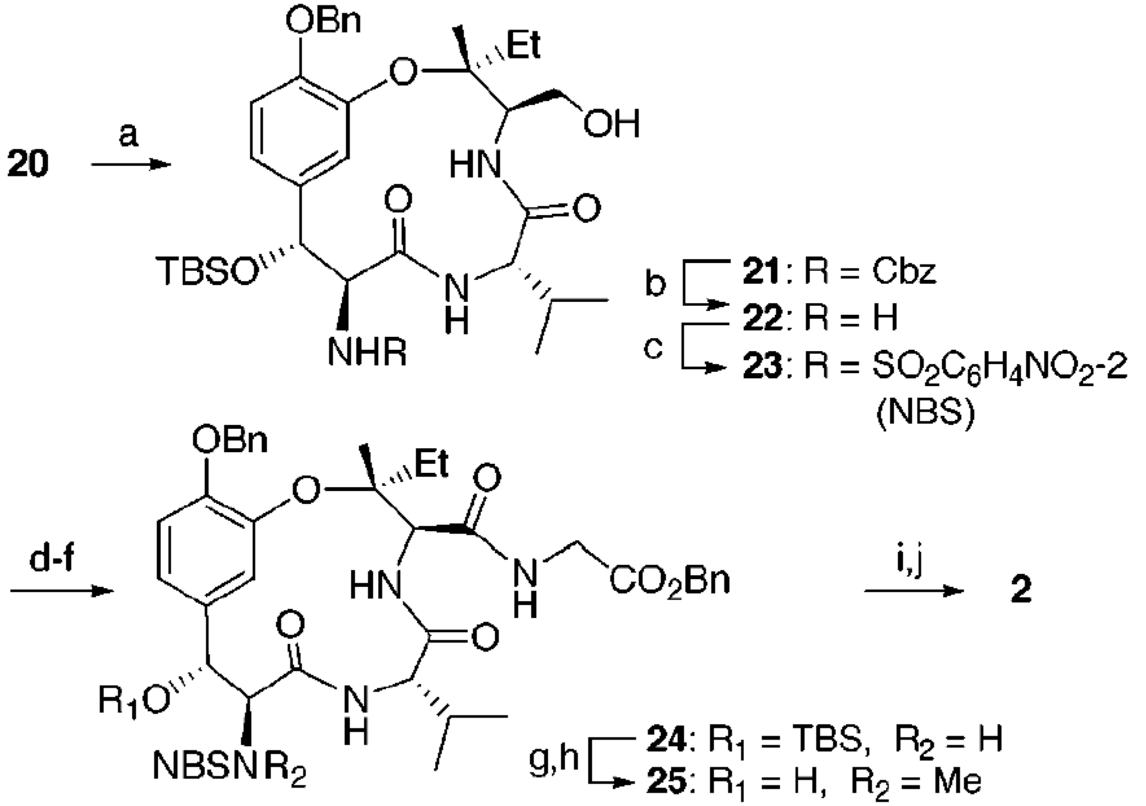
17: R_1 = H, R_2 = Et, R_3 = CO_2t-Bu

18: R_1 = TBS, R_2 = Et, R_3 = CO_2TBS

19: R_1 = TBS, R_2 = H, R_3 = H

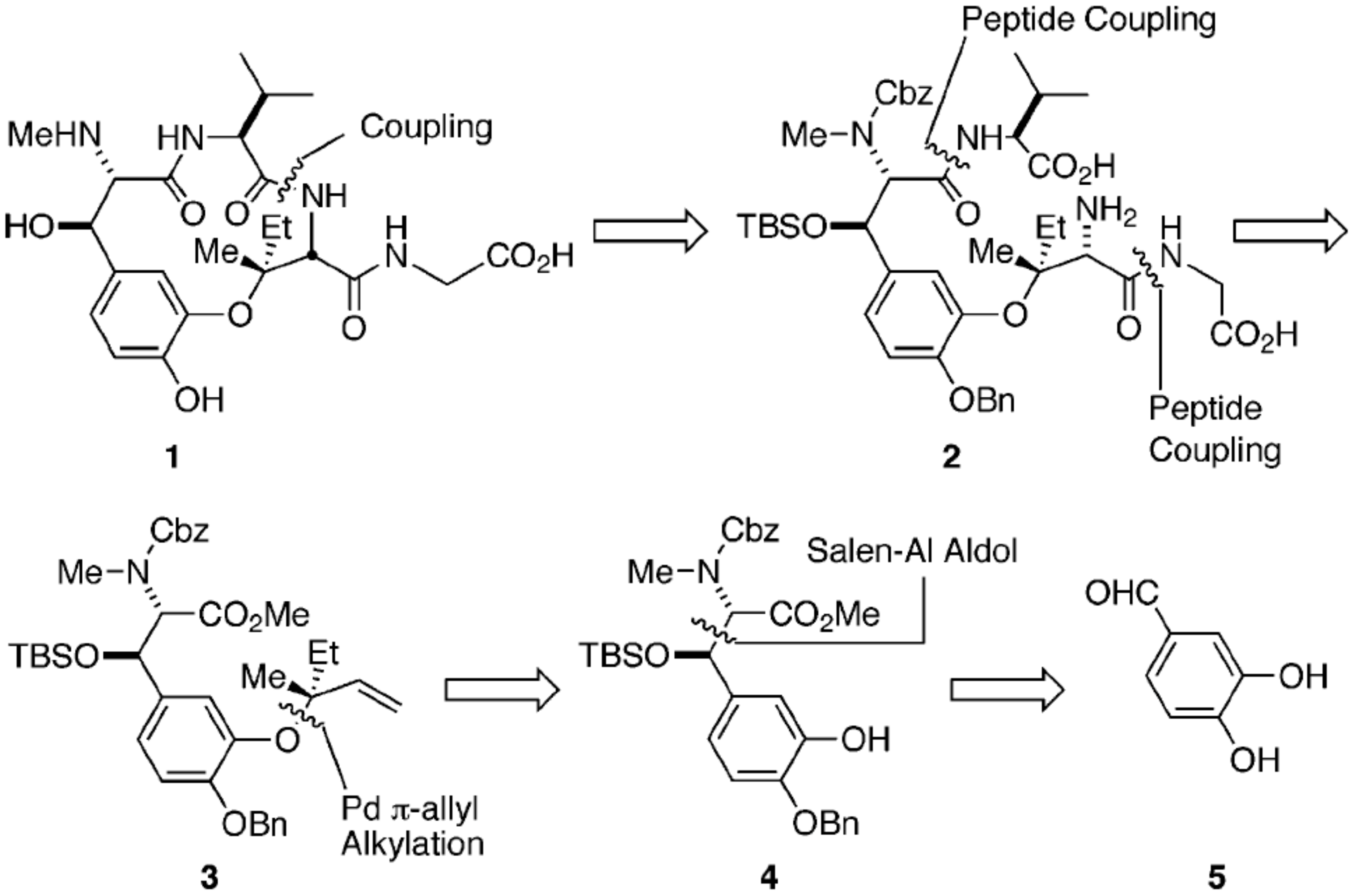
K_2CO_3, *n*-Bu_4NI, DMF, 96%; (o) ethyl acrylate, $Pd(OAc)_2$, (*o*-tolyl)$_3$P, Et_3N, CH_3CN, reflux, 6 h, 95%; (p) NaOH, $BnOCONH_2$, *t*-BuOCl, $K_2[OsO_2(OH)_4]$, $(DHQD)_2AQN$, *n*-PrOH:H_2O (1:1), 20 °C, 1 h, 58%; (q) TFA, CH_2Cl_2, 0 °C; (r) *N*-Boc-L-valine•OH, DEPBT, *i*-Pr_2NEt, THF, 81% for 2 steps; (s) 6 equiv of TBSOTf, 8 equiv of 2,6-lutidine, CH_2Cl_2, room temperature; (t) LiOH, *t*-BuOH−H_2O, 83% for 2 steps; (u) 5 equiv of EDCI•HCl, 5 equiv of HOBt, DMF−CH_2Cl_2 (1:5), 0 °C to room temperature, 78%.

Joullie's Completion of Ustiloxin D-First Generation

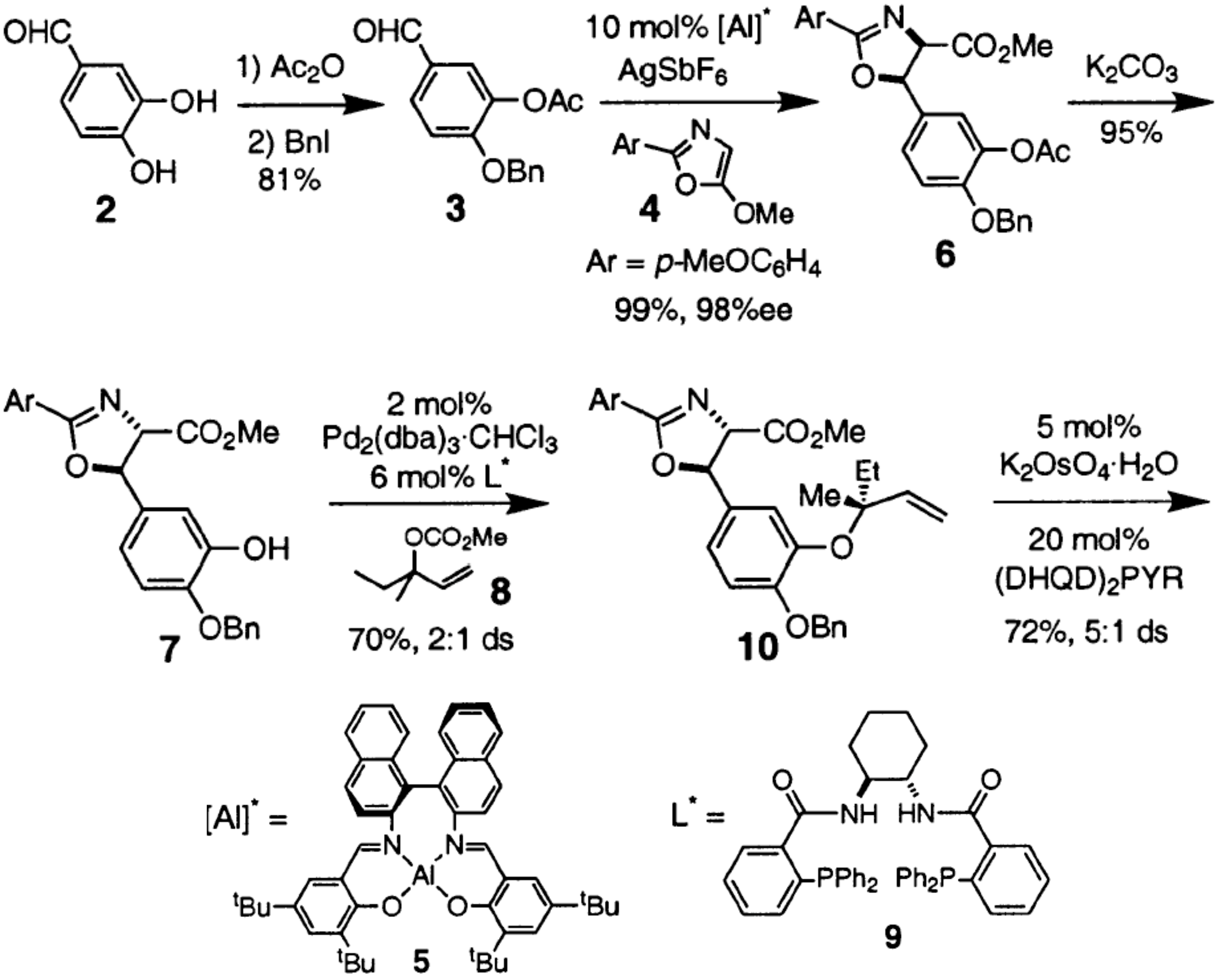


[a] Key: (a) *B*-bromocatecholborane, CH_2Cl_2, −78 °C, 88%; (b) H_2, 5% Pd/C, 2,2′-dipyridyl, MeOH−EtOAc, 2 h; (c) 2-nitrobenzenesulfonyl chloride, 2,4,6-collidine, 85% for 2 steps; (d) Dess−Martin periodinane, CH_2Cl_2; (e) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH−H_2O; (f) Gly·OBn, DEPBT, *i*-Pr_2NEt, THF, 66% for 3 steps; (g) methyl 4-nitrobenzenesulfonate, MTBD, DMF, 77%; (h) *n*-Bu_4NF−HOAc (1:1.1), THF, 0−25 °C, 4 h, 96%; (i) $HSCH_2CH_2OH$, DBU, DMF, room temperature, 74%; (j) H_2, Pd black, EtOH−H_2O, 1.6 equiv of HCl, 2 h, 85%.

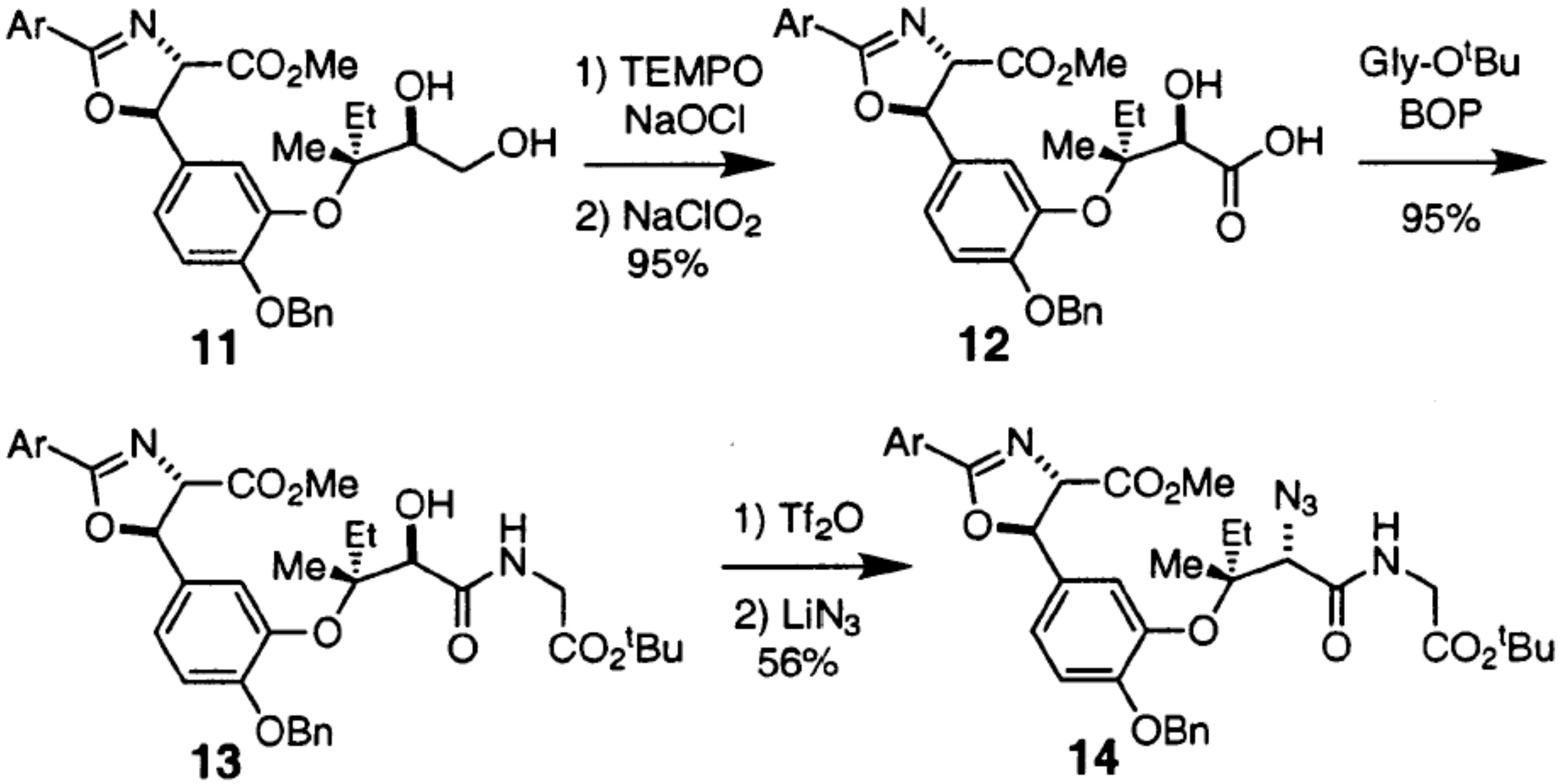
Wandless Retrosynthetic Analysis of Ustiloxin D



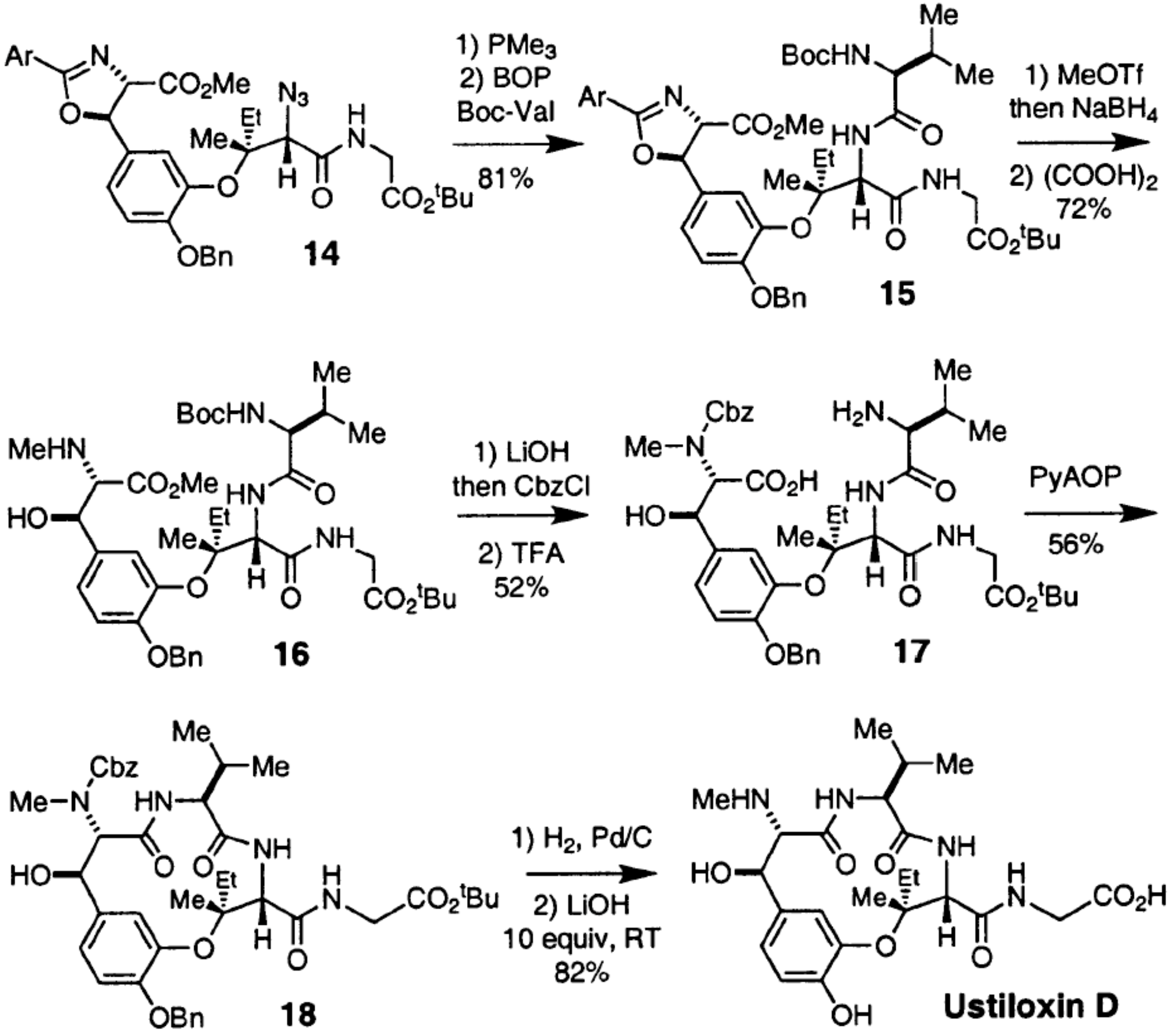
Wandless Synthetic Approach



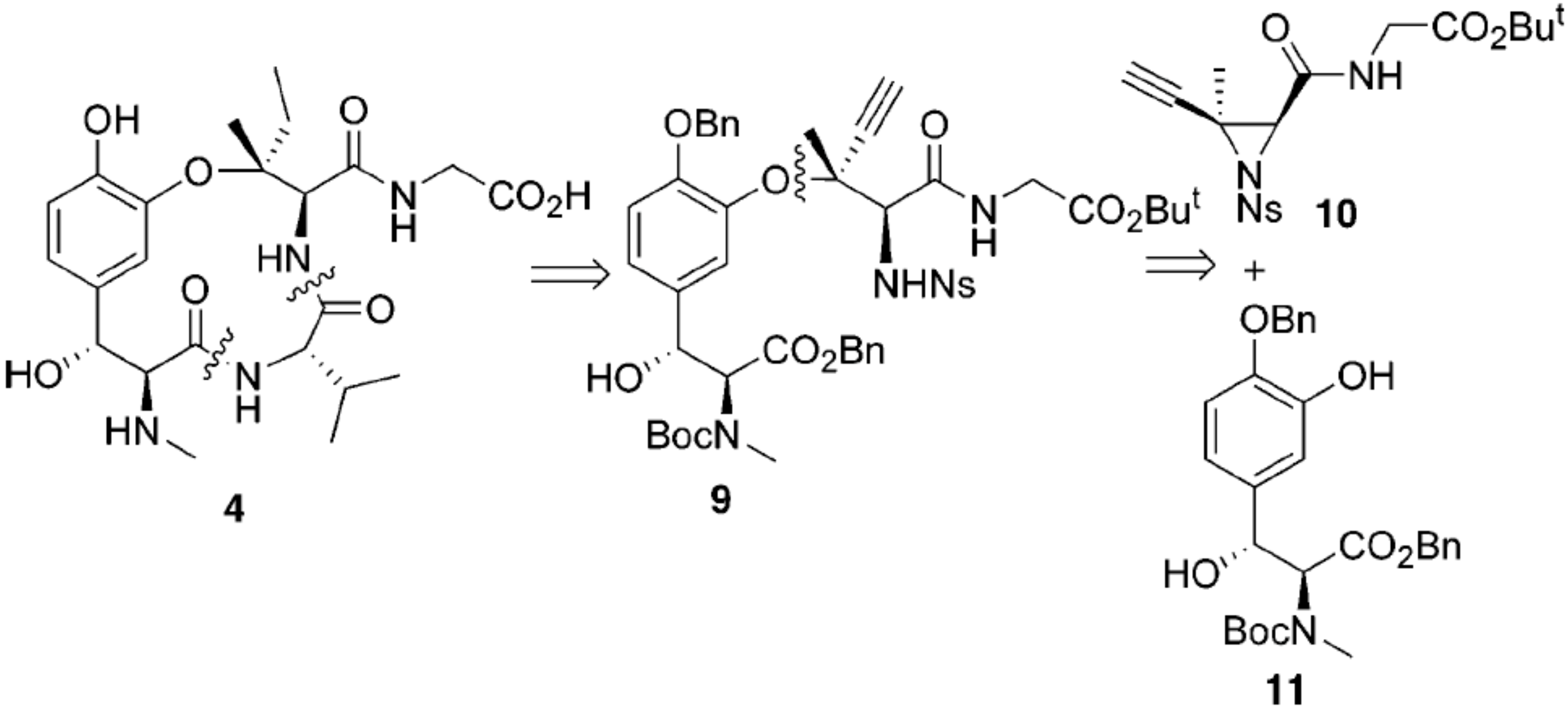
Wandless Synthetic Approach Continued



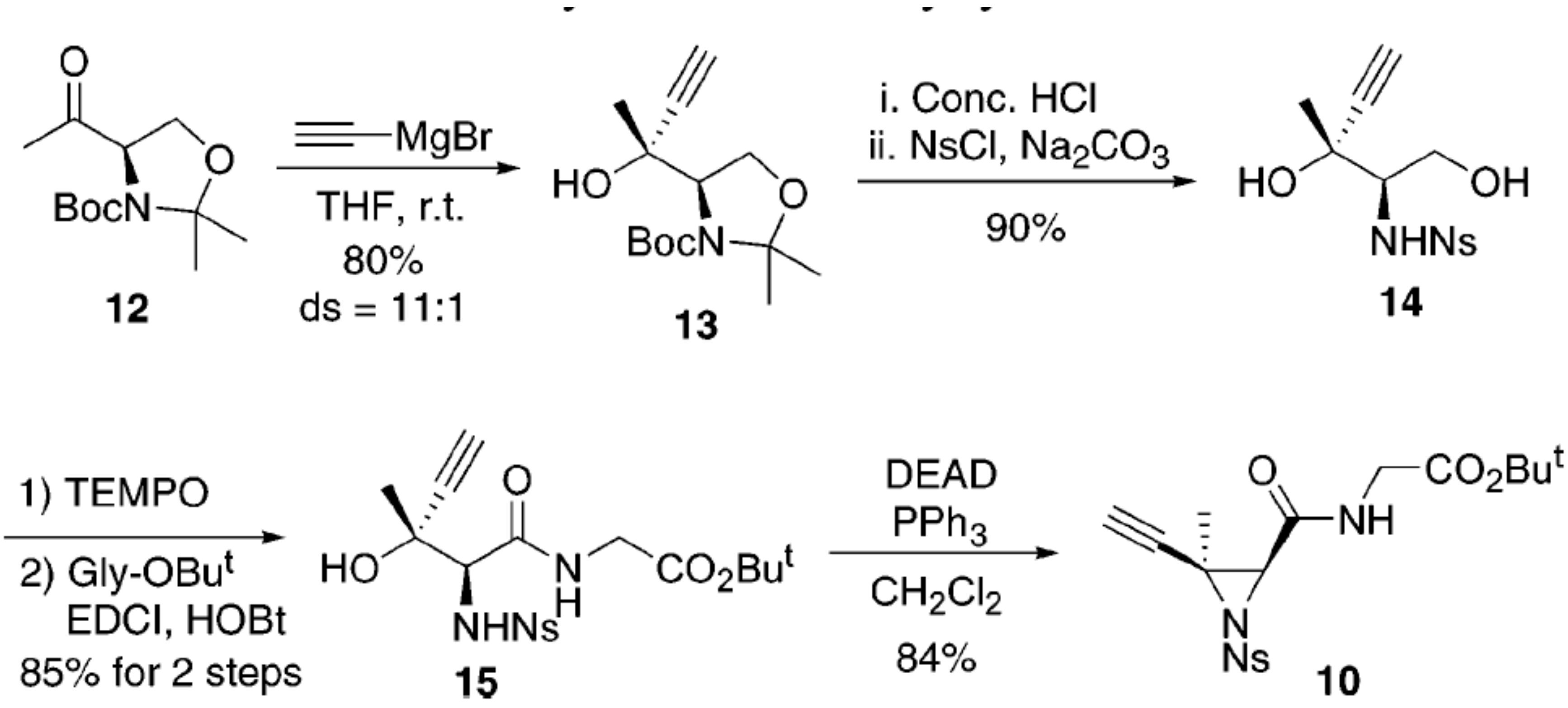
Wandless Completion of Ustiloxin D



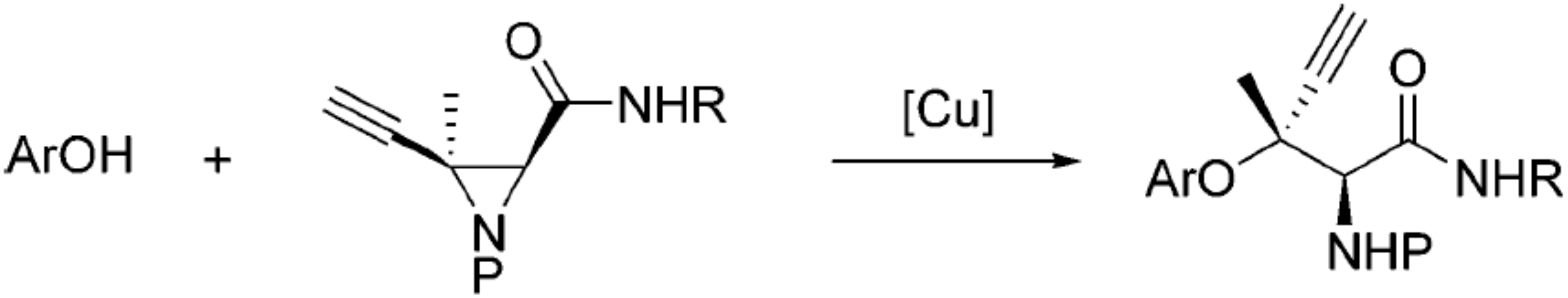
Joullie's Second Retrosynthetic Analysis of Ustiloxin D



Joullie's Second Generation Synthetic Approach



Copper-Catalyzed Ethynyl Aziridine Ring Opening By Phenol Derivatives



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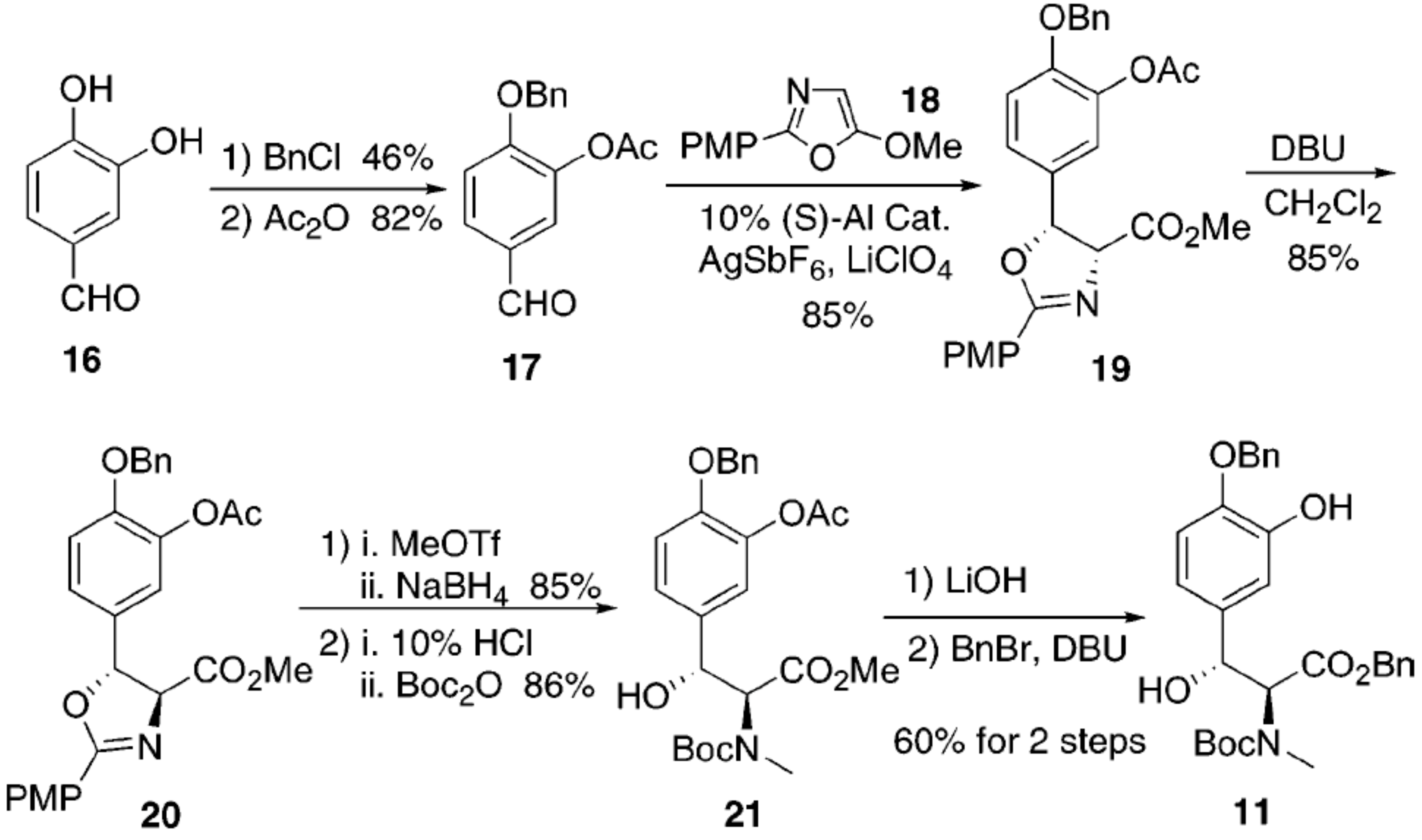
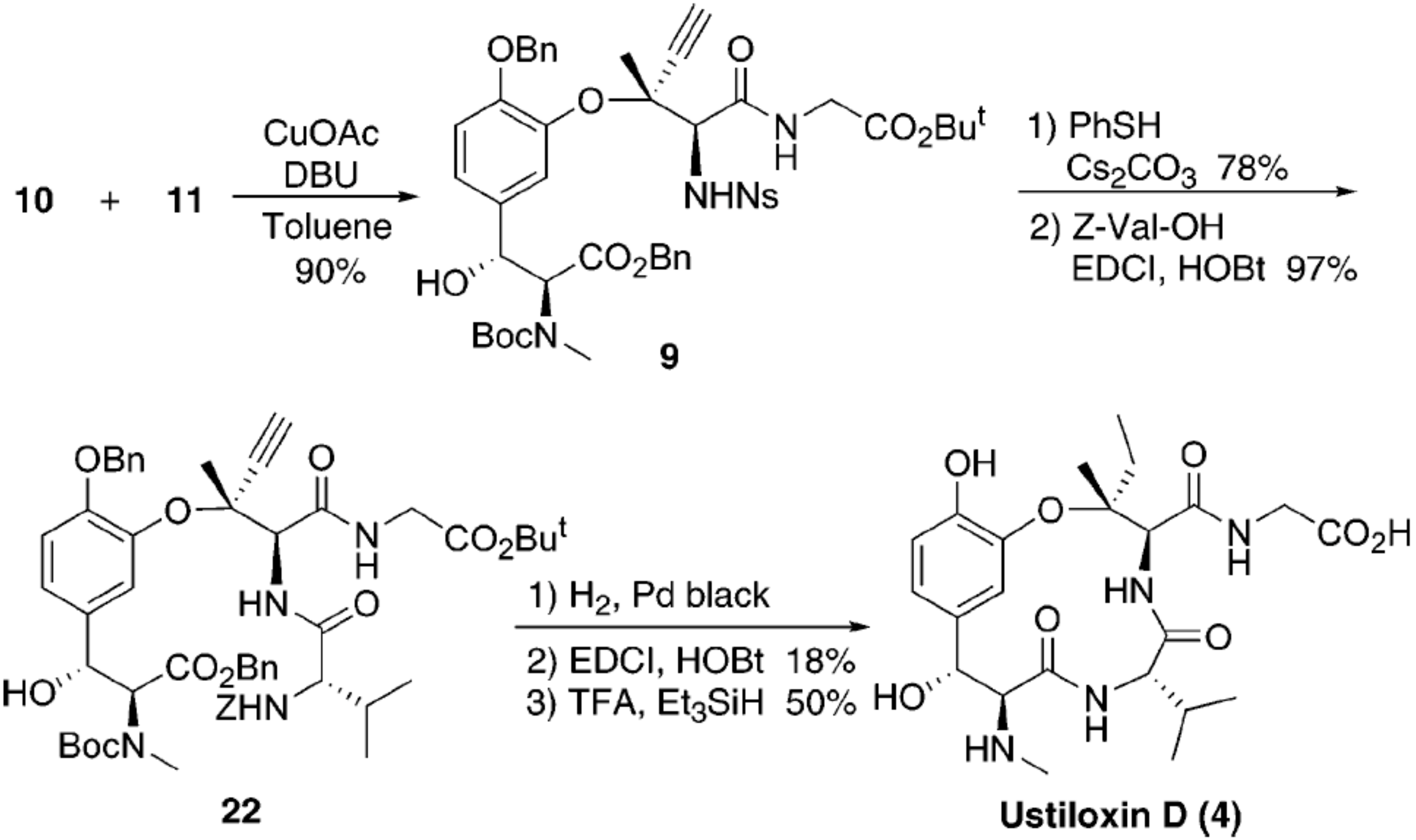
Synthesis of b-Hydroxyl Tyrosine Derivative **11**



Joullie's Completion of Ustiloxin D-Second Generation



Conclusions

- The total synthesis of ustiloxin D was accomplished in 31 steps by Joullie utilizing a (S_NAr) reaction to construct the chiral alkyl-aryl ether.

- The second total synthesis of ustiloxin D was accomplished in 20 steps by Wandless utilizing an Evan's Al catalyzed asymmetric aldol-type reaction as well as a Trost AAA reaction to construct the chiral alkyl-aryl ether.

- The third total synthesis of ustiloxin D was accomplished in 15 steps by Joullie utilizing an unprecedented ethynyl aziridine ring opening by a b-hydroxy tyrosine derivative.