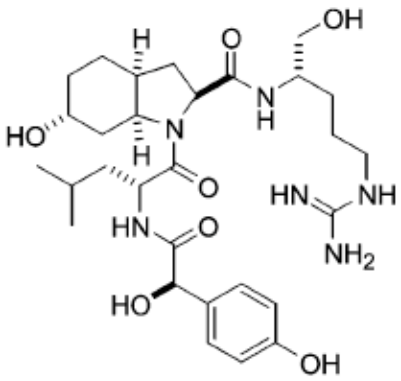
The N-Acyloxyiminium Ion Aza-PrinsRoute to Ocathydroindoles: Total Synthesis and Structural Confirmation of the Antithrombotic Marine Natural Product Oscillarin

Hanessian, Stephen, et. al. *J. Am. Chem. Soc.* **2004**, 126, 6064-6071

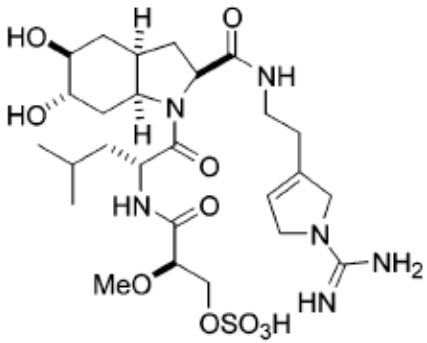
Literature Presentation

July 29, 2004

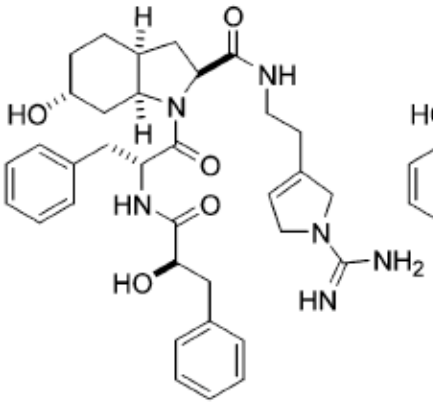
Aeruginosins



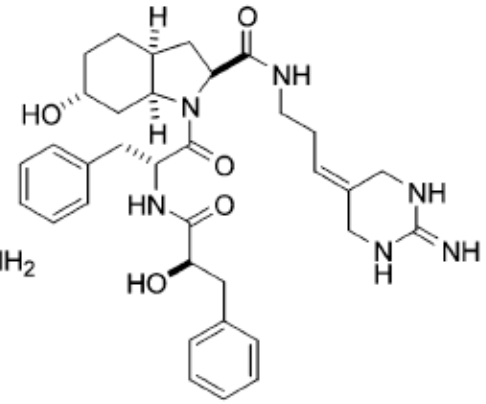
Aeruginosin 298-A



Dysinosin A, **1**



Oscillarin (D-Pla-D-Phe-L-Choi-Adc), **2**
(actual structure)

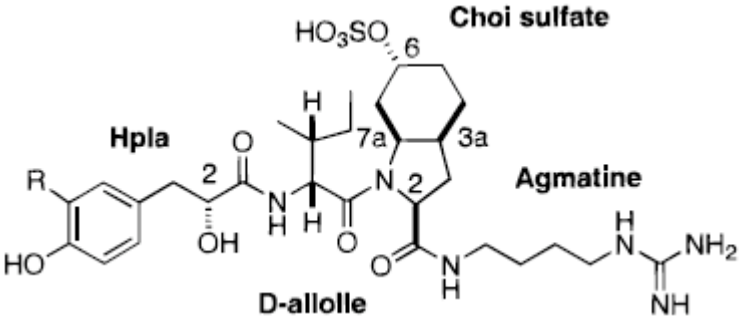


Oscillarin, **2a**
(originally proposed structure)

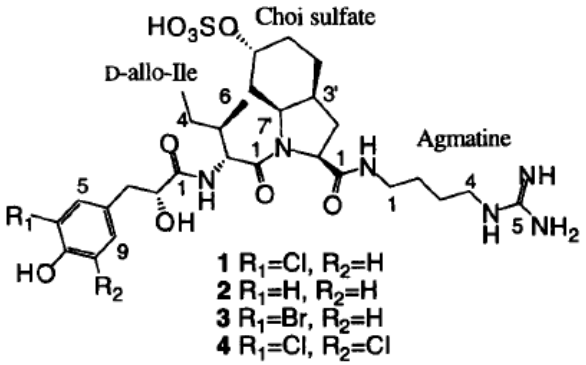
Figure 1. Structures of aeruginosin 298A, dysinosin A **1**, oscillarin (D-Pla-D-Phe-L-Choi-Adc) **2** and an originally presumed structure **2a**.

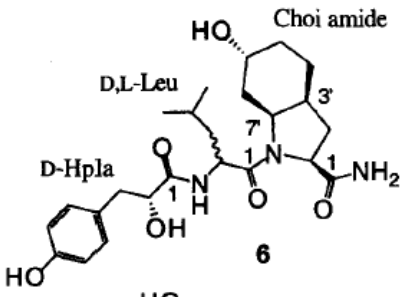
-First isolated from *Microcystis aeruginosa* (Aeruginosa 298-A)
-A common feature of the Aeruginosa family is 1-aza[4.3.0]-bicyclic core (**ocatahydroindole 2-carboxylic acid core**)
-Show Serine Protease inhibitory activity

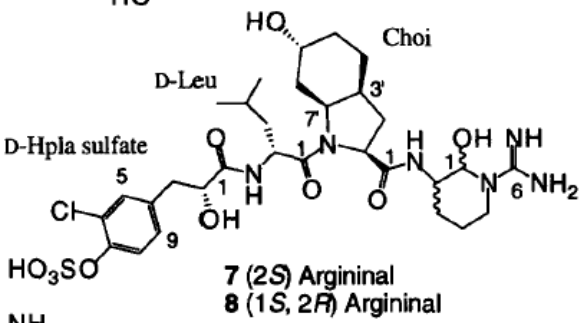
Aeruginosins

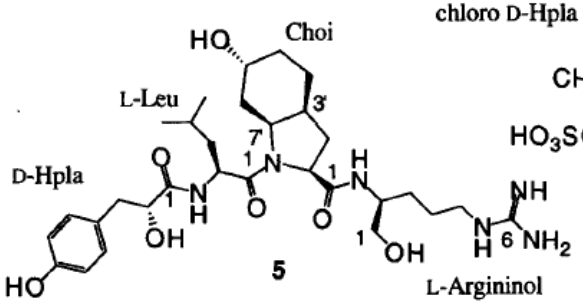


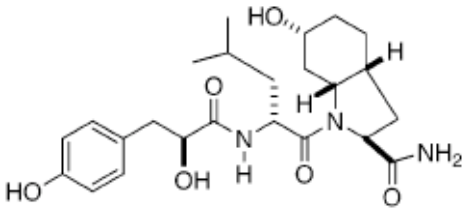
Aeruginosin 98-A and -B











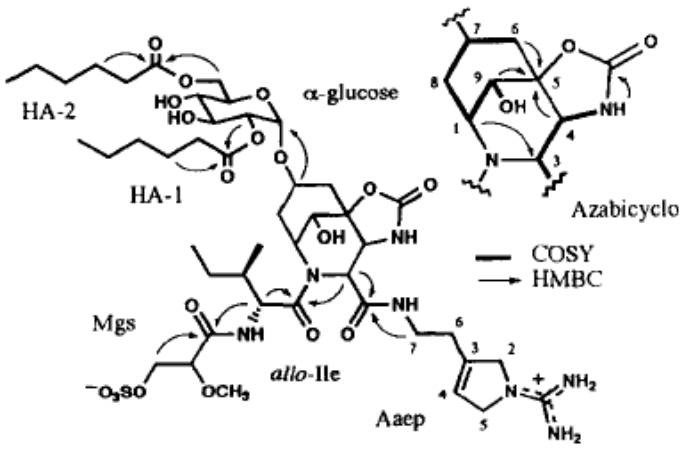
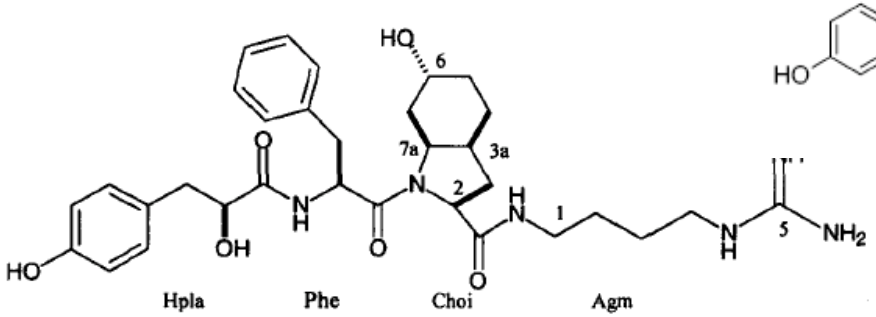
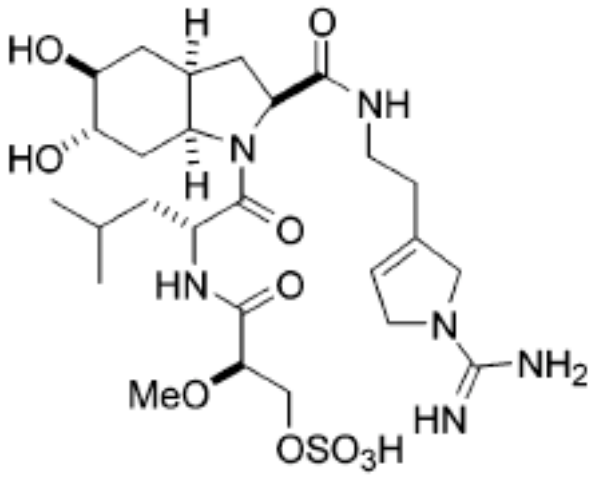


Fig. 1. Structure of suomilide (**1**).



Microcin SF608 (**3**)

Dysinosin A

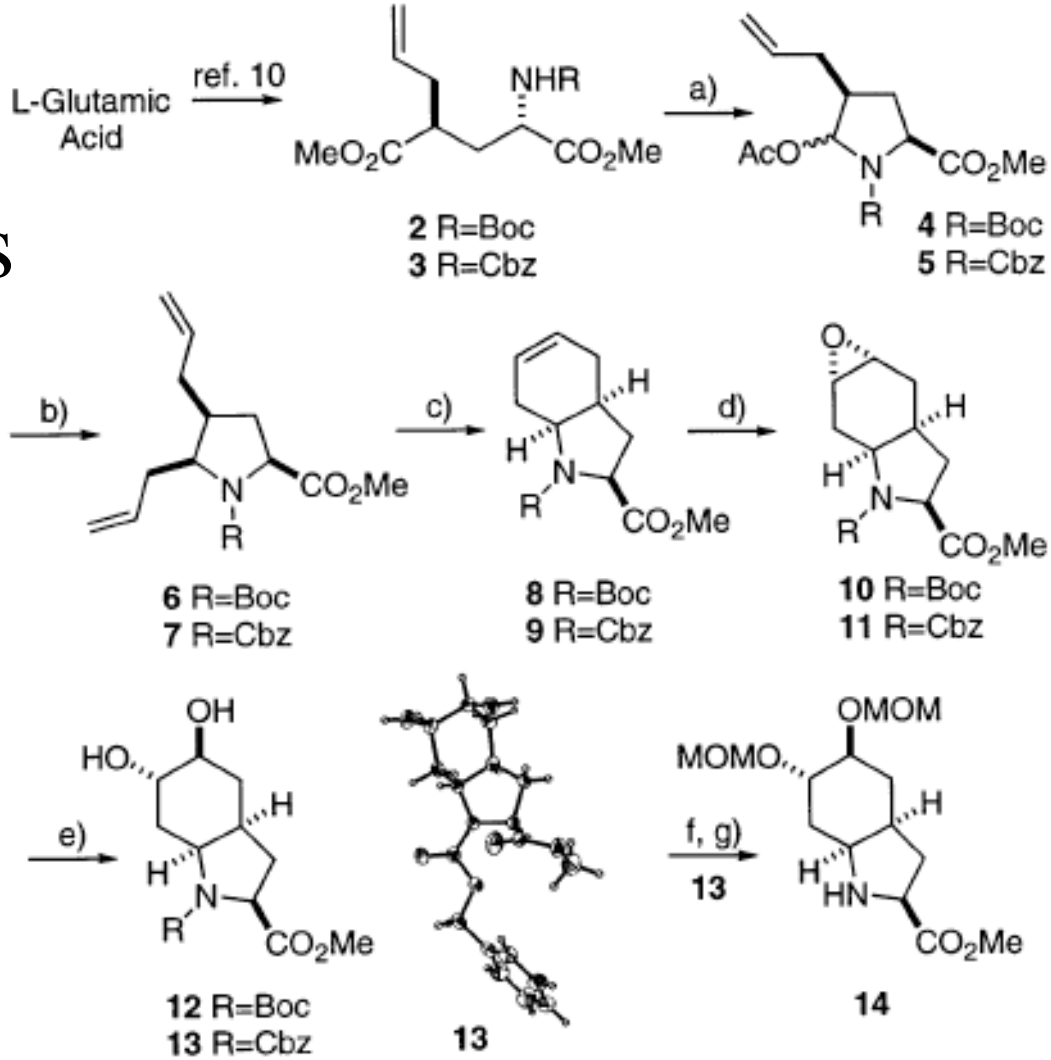


Dysinosin A, **1**

-From a new genus of sponge of the family *Dysideidae* (Lizard Island, Queensland, Australia)
-Inhibitory activity against thrombin and Factor VIIa (esential components in the blood coagulation cascade)
-Differs from Aeruginosins by: 5S, 6S-diol, 1(N-amidino-Δ^3-Pyrrolino)-ethyl side chain, and O-sulfylated D-glyceric acid

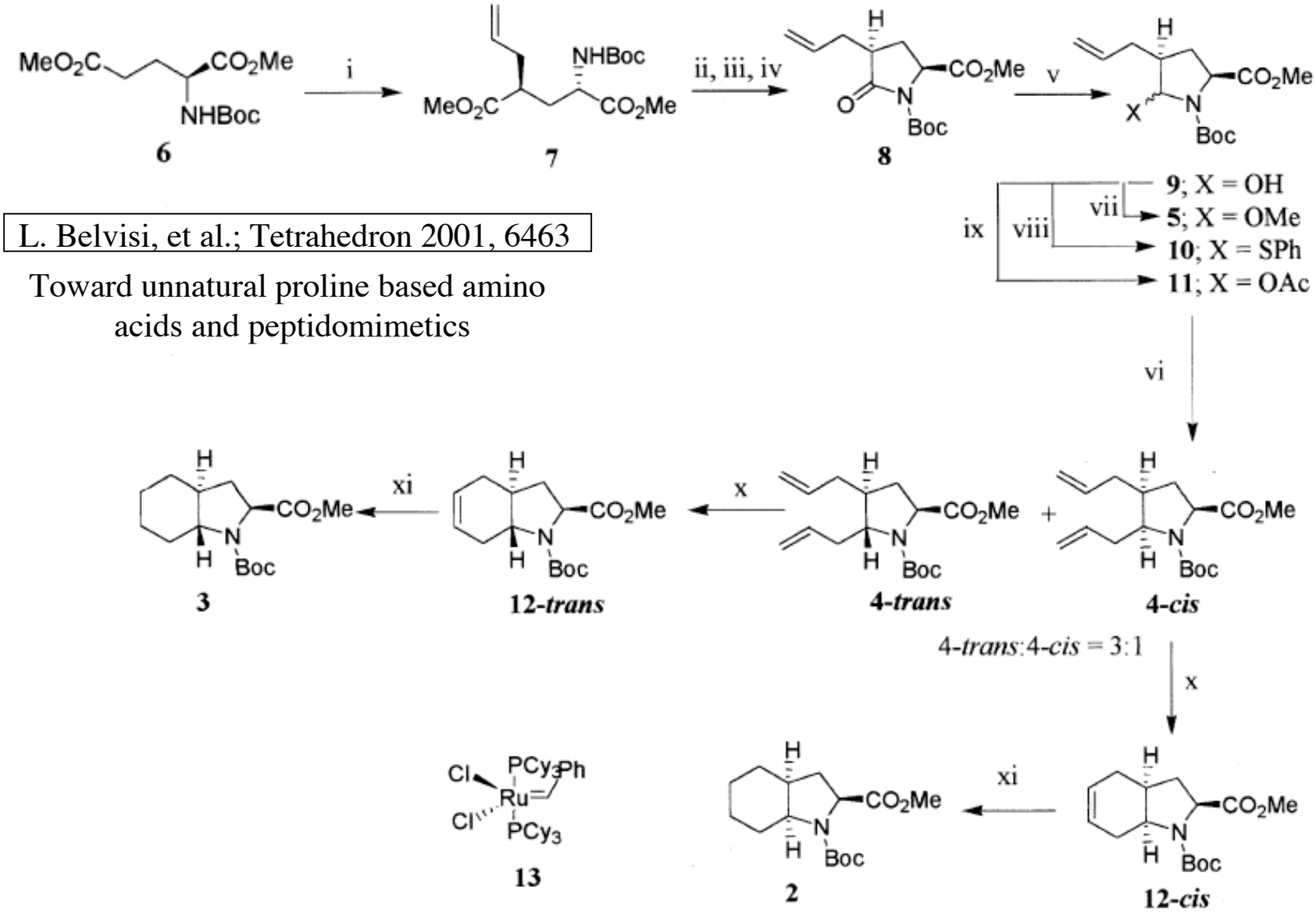
Previous Preparation of Octahydroindoles …Toward Dysinosin A

Hanessian, et al.; JACS 2002, 13343



[a] Reagents and conditions: (a) 1. TFA, CH_2Cl_2; 2. $NaHCO_3$; 3. Δ, toluene; 4. LiHMDS, CbzCl, THF −78 °C; 5. $LiHBEt_3$, THF −78 °C; 6. Ac_2O, DMAP, CH_2Cl_2; overall 85%. (b) $BF_3.OEt_2$, allyl tributylstannane, toluene −78 °C (*syn*/*anti* 5.5:1); overall 83%. (c) Ru benzylidene$(Cy_3P)_2Cl_2$ 1 mol %, CH_2Cl_2; 99%. (d) *m*-CPBA, CH_2Cl_2. (e) TFA (0.2 equiv),THF/H_2O (1/1); 75−79% (2 steps). (f) MOMCl, $(^iPr)_2NEt$, CH_2Cl_2; 98%. (g) Pd/C 20%, H_2,MeOH; 95%.

Previous Preparation of Octahydroindoles

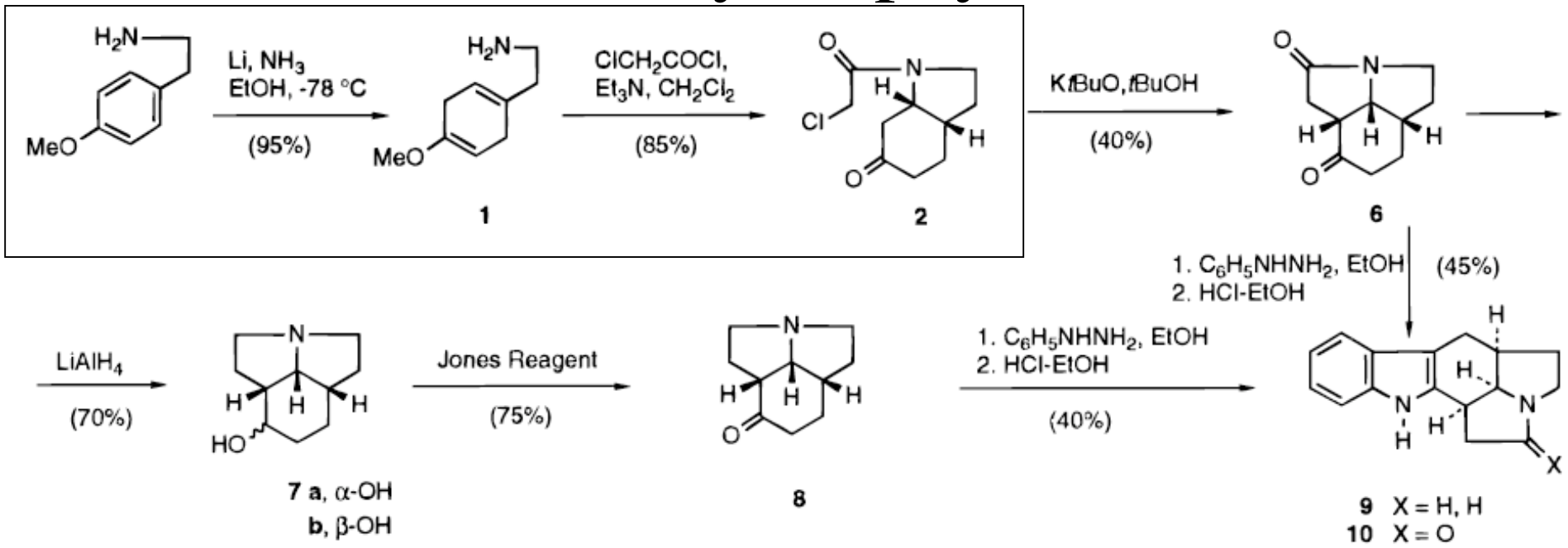


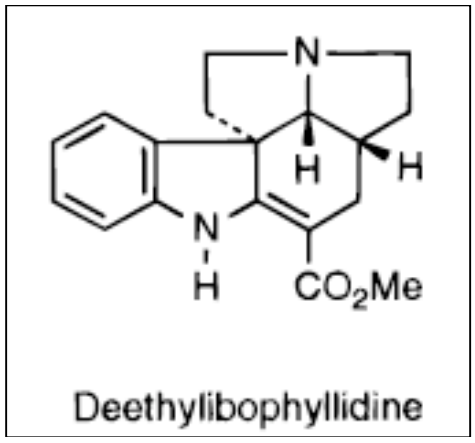
L. Belvisi, et al.; Tetrahedron 2001, 6463

Toward unnatural proline based amino acids and peptidomimetics

Scheme 3. i: HMDS, BuLi, allyl bromide, THF, 72%; ii: TFA, CH_2Cl_2, 0°C; iii: toluene, 110°C, 85% over two steps; iv: Boc_2O, DMAP, THF, 98%; v: $LiEt_3BH$, THF, −78°C, 91%; vi: Allyl tributyltin, *tert*-butyldimethylsilyl trifluoromethanesulphonate, −78°C, 75%; x: Grubbs catalyst, CH_2Cl_2, 91%; xi: H_2, Pd/C, EtOH, 95%.

Previous Preparation of Octahydroindoles… Fischer Indolelization Route to (±)-Deethylibophyllidine

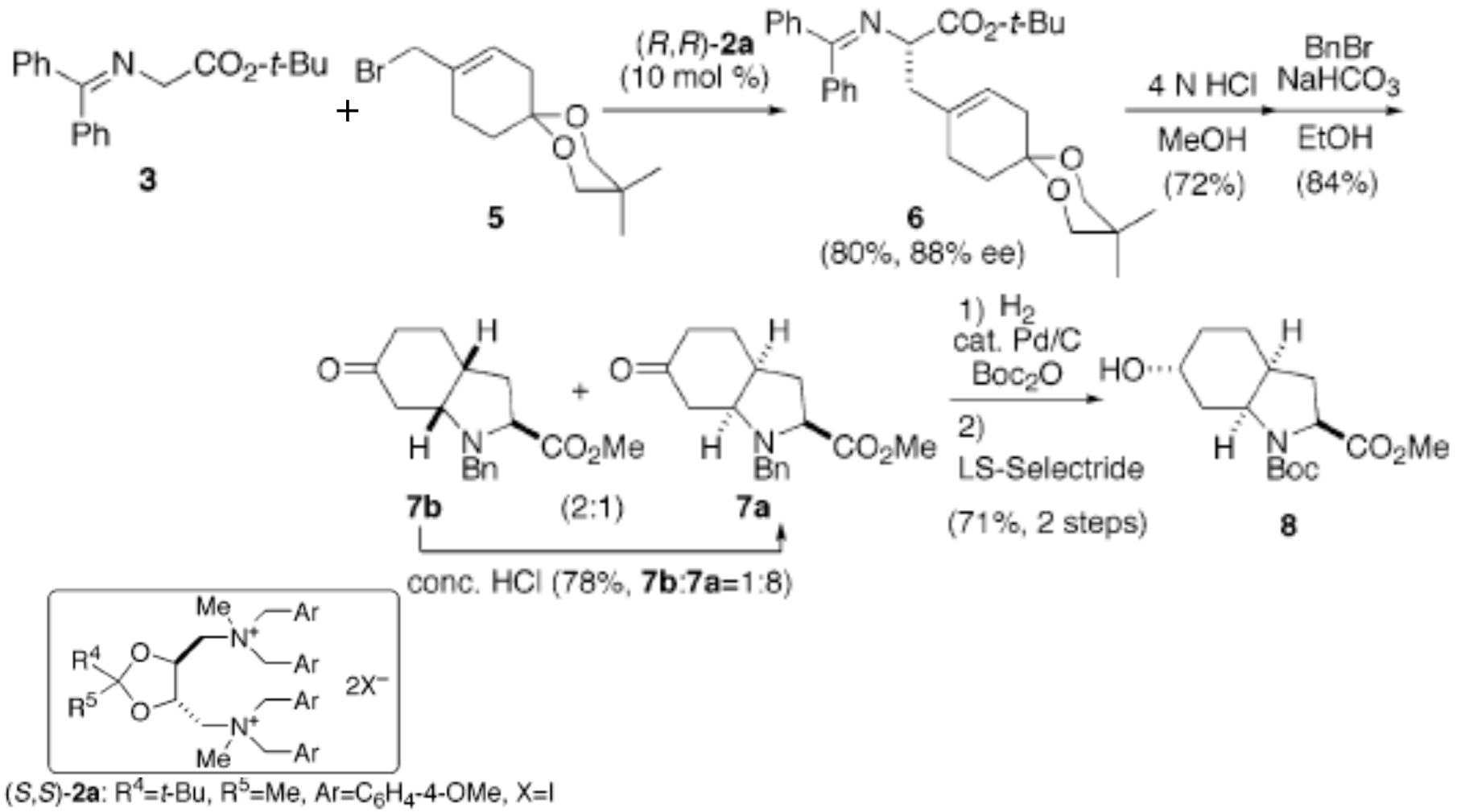




Deethylibophyllidine

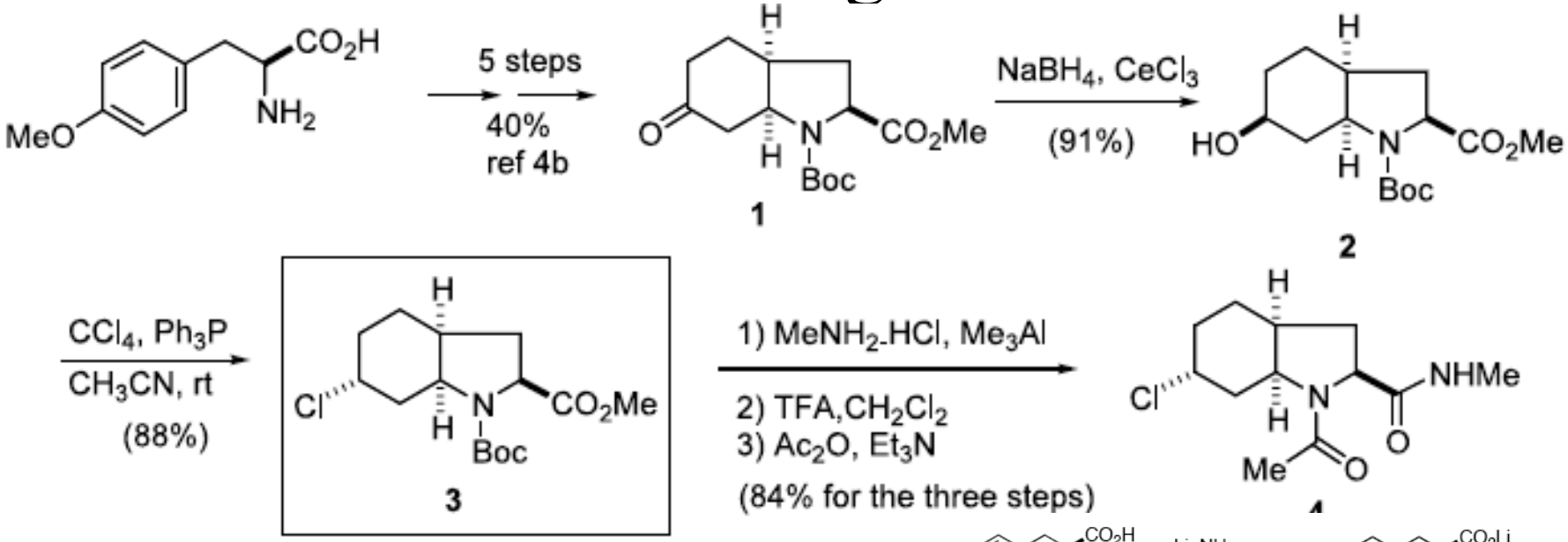
J. Bonjoch, et al.; *J. Org. Chem.* **1996**, 61, 1706-1715

Previous Preparation of Octahydroindoles …Towards Aeruginosin 298-A

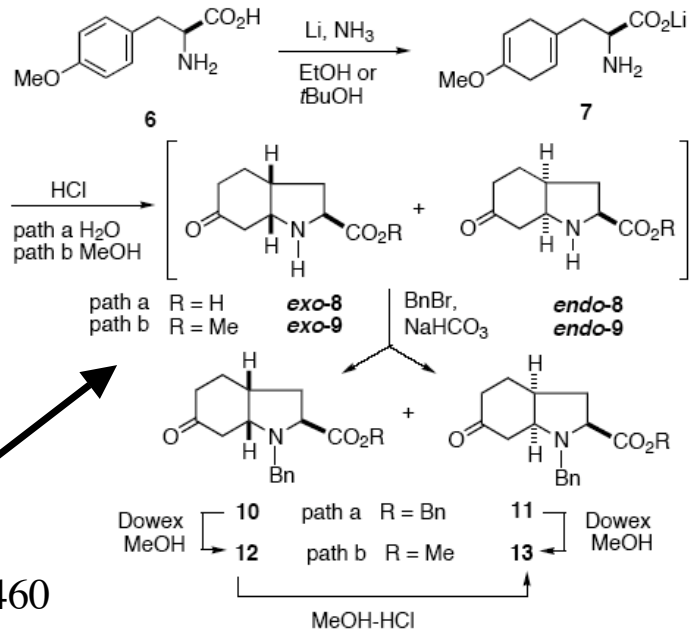


M. Shibasaki, et al. *J. Am. Chem. Soc.* **2003**, 125, 11206-11207

Previous Preparation of Octahydroindoles …Towards Aeruginosins 205

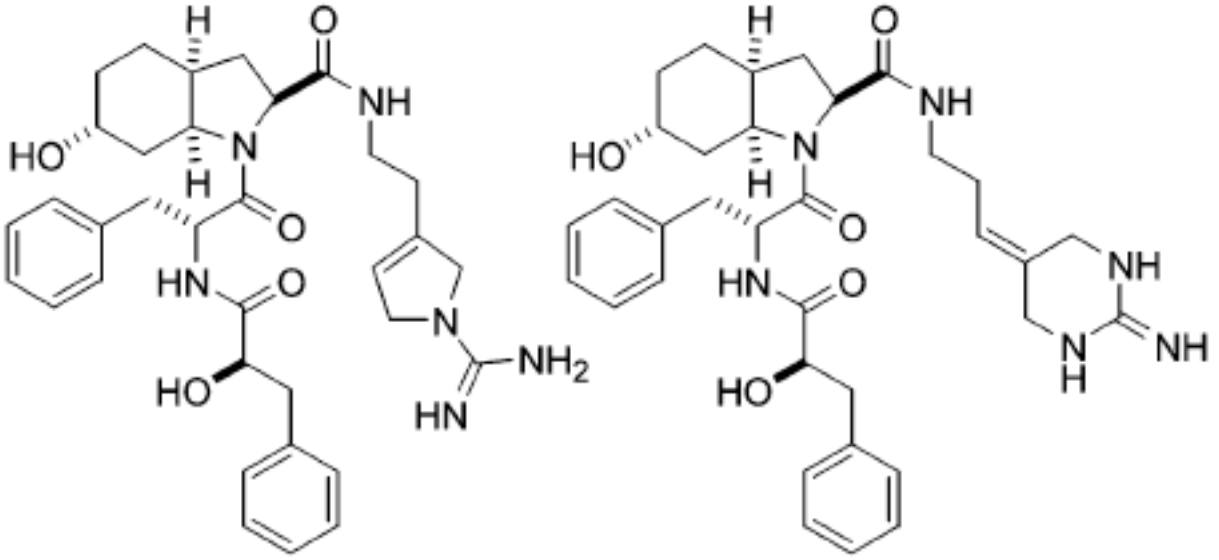


N. Valls, et al. *Tetrahedron: Asym.* **2003**, 14, 1241-1244



N. Valls, et al.; *Chem. Eur. J.* **2001**, 7, 3446-3460

Oscillarin



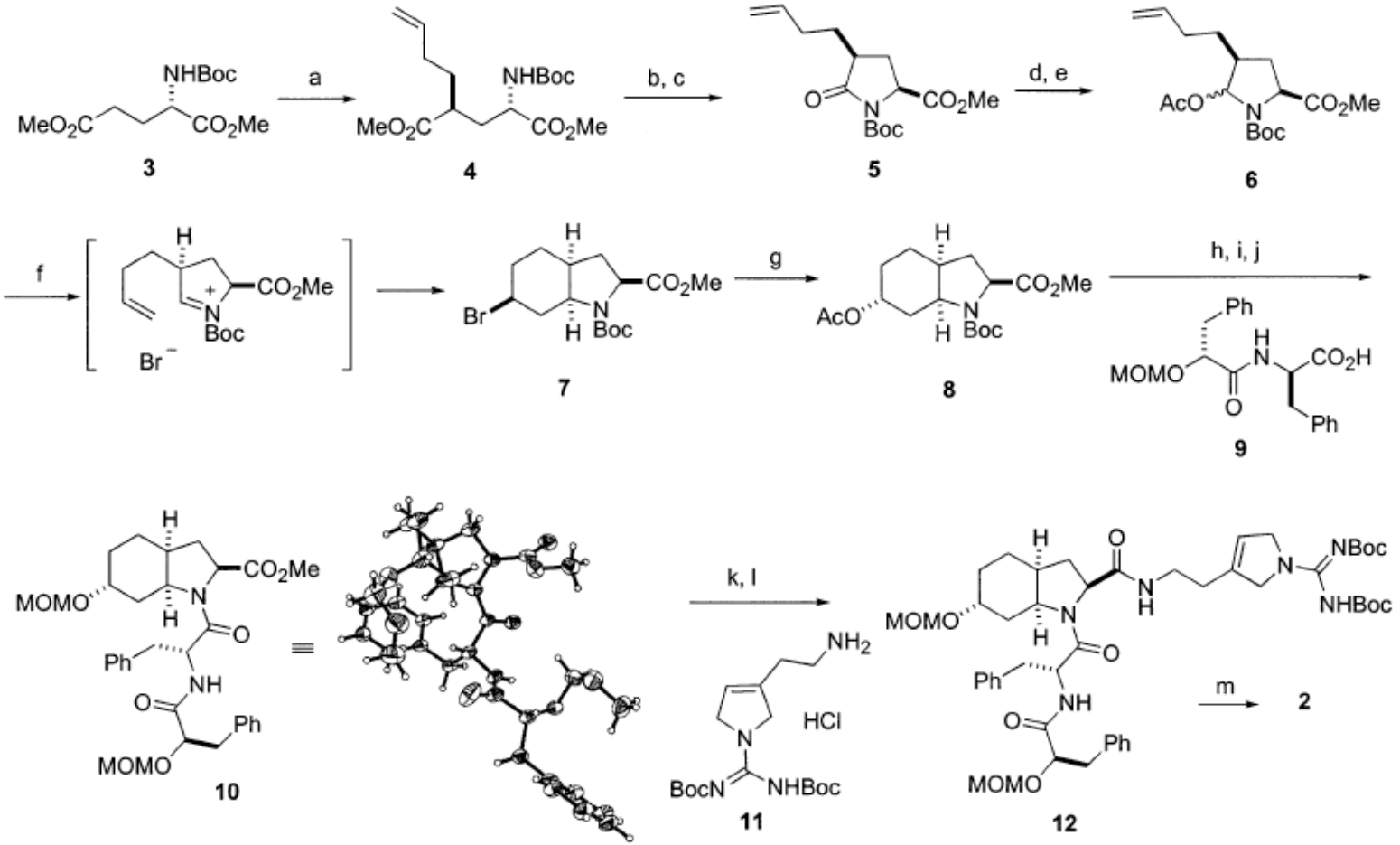
Oscillarin (D-Pla-D-Phe-L-Choi-Adc), **2**
(actual structure)

Oscillarin, **2a**
(originally proposed structure)

Isolated from algal cultures of *Oscillatoria agardhii* (strain B283)
(at University of Gottingen)

Hanessian, Stephen, et. al. *J. Am. Chem. Soc*. **2004**, 126, 6064-6071

Synthesis of Oscillarin



[a] a: LiHMDS, THF, −78 °C, then 3-butenol triflate, 85%; b: TFA, CH_2Cl_2 then toluene reflux, 92%; c: Boc_2O, Et_3N, DMAP, CH_2Cl_2, 90%; d: $LiBHEt_3$, THF, −78 °C; e: Ac_2O, Et_3N, DMAP, CH_2Cl_2, 91% (two steps); f: $SnBr_4$, CH_2Cl_2, −78 °C, 78%; g: Bu_4NOAc, toluene, 40−50 °C, 78%; h: TFA, CH_2Cl_2, then EDC, HOBt, **9**, CH_2Cl_2, 91% (two steps); i: NaOMe/MeOH; j: MOMCl, $^iPr_2NEt$, CH_2Cl_2, 80% (two steps); k: LiOH, H_2O/THF; l: EDC, HOBt, Et_3N, **11**, 86% (two steps); m: aq HCl/THF 6N, 70%.

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Synthesis of Original Oscillarin

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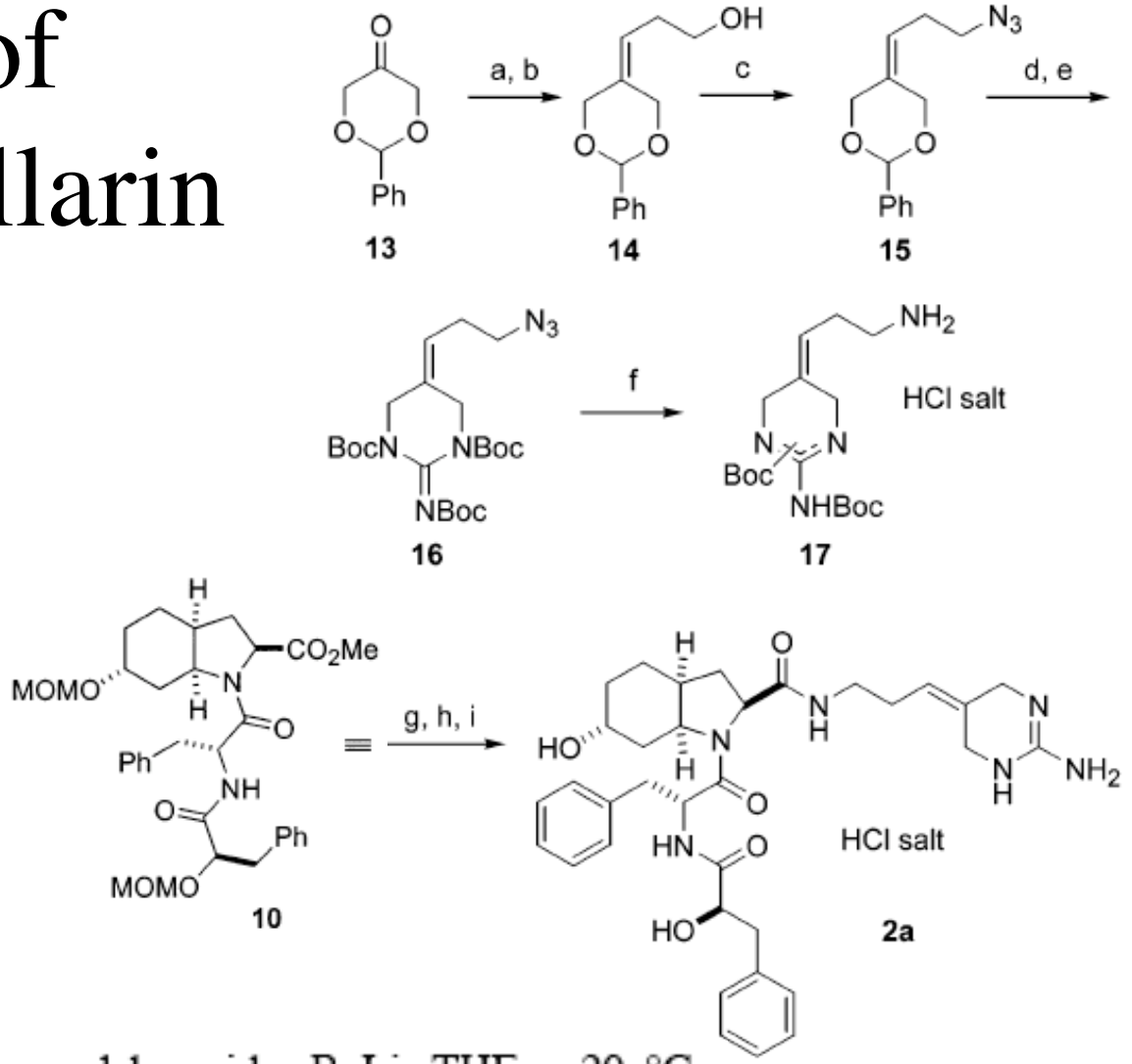
J. Am. Chem. Soc. **2004**, 126, 6064-6071



[a] a: 3-triphenylphosphoniumpropanol bromide, BuLi, THF, −20 °C, TMSCl, then **13**; b: TBAF, THF, 75%; c: MsCl, $^{i}Pr_2NEt$, CH_2Cl_2, then NaN_3, DMF, 50 °C, 85%; d: AcOH (80% in water); e: DEAD, PPh_3,CH_2Cl_2, tris(Boc)guanidine, 50% (two steps); f: PPh_3, H_2O, then AcOH, then Dowex 1 × 8−50 (Cl^-), 60%; g: LiOH, H_2O/THF; h: EDC, HOBt, Et_3N, **17**, 70% (two steps); i: aq HCl/THF 4N, 60%.

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Thrombin-Oscillarin Complex

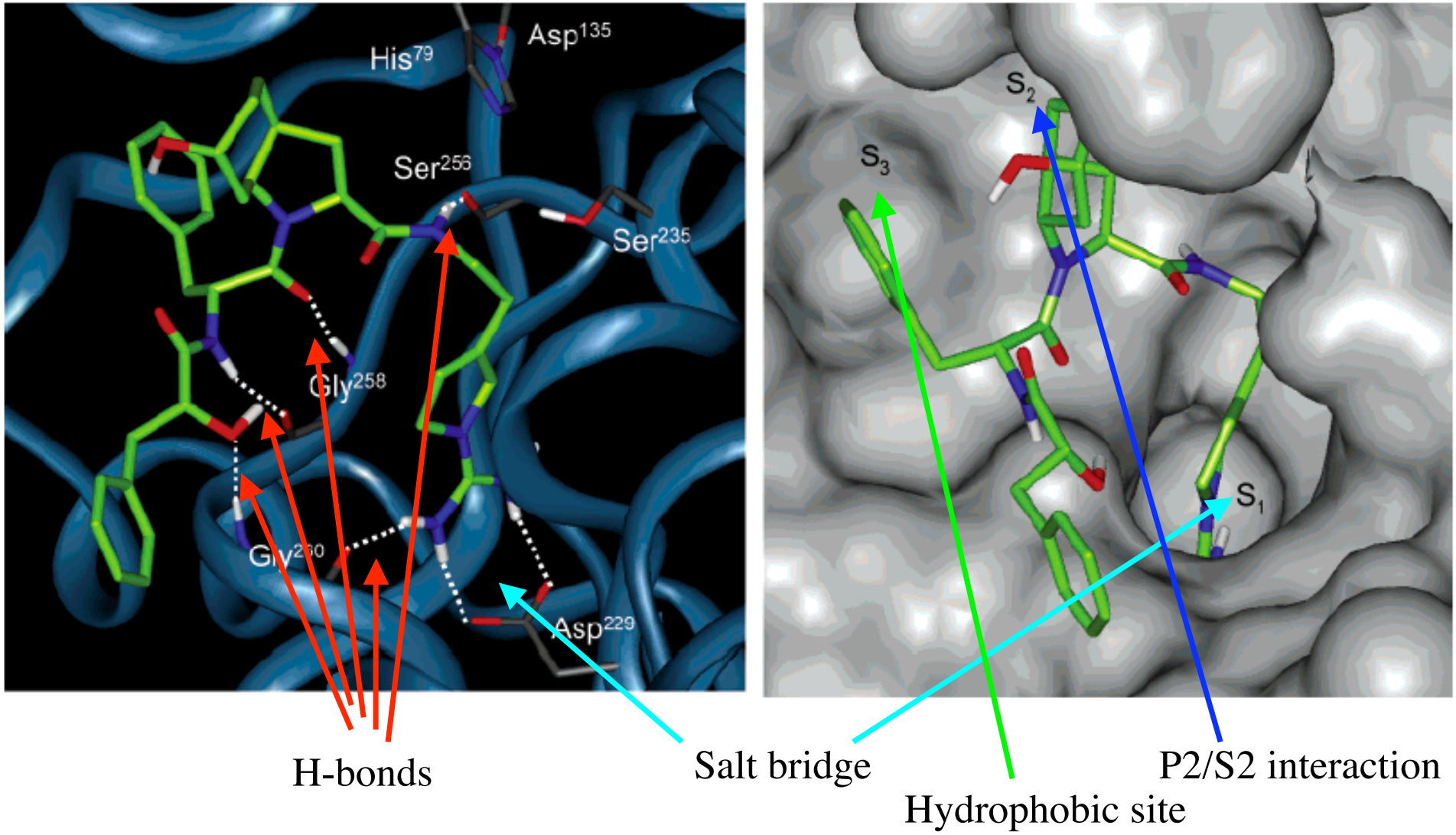

Figure 2. Left: Ribbon representation of thrombin-oscillarin complex at 2.0 Å resolution. Right: Connolly surface representation of thrombin-oscillarin complex.

Aza-Prins-N-acyliminium ion type cyclizations

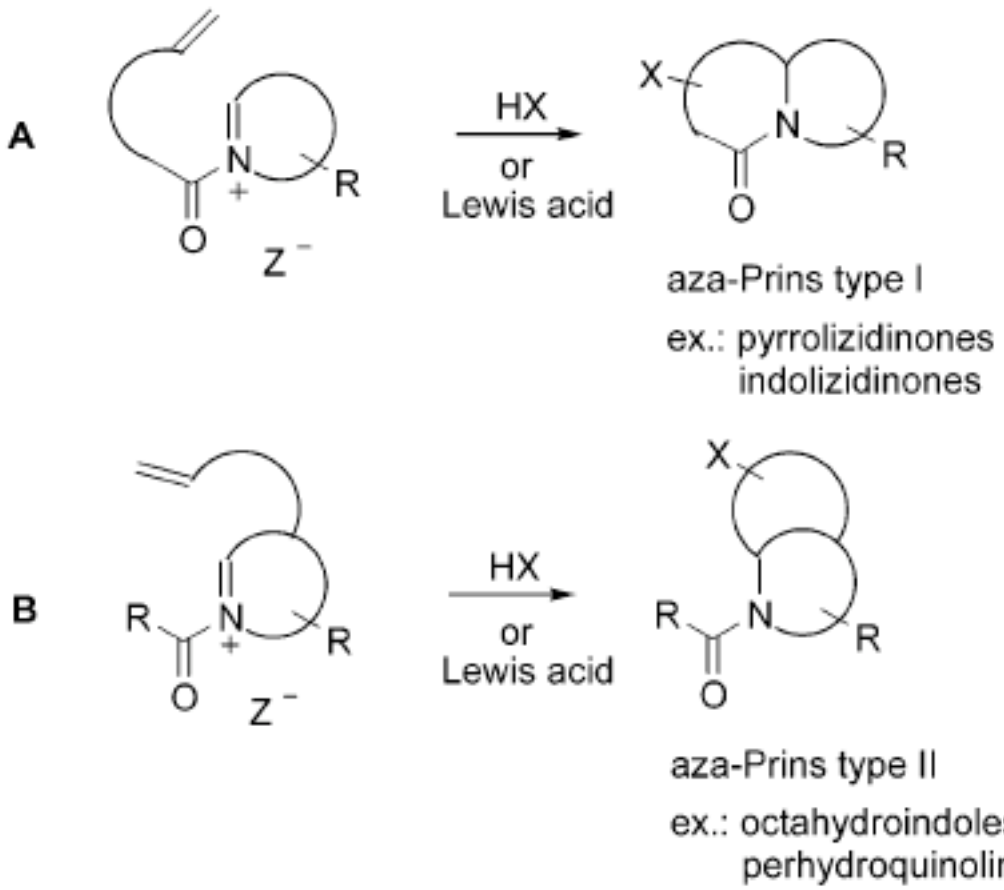

Figure 3. *N*-Tethered (A) and *C*-tethered (B) intramolecular aza-Prins-*N*-acyliminium ion type cyclizations.

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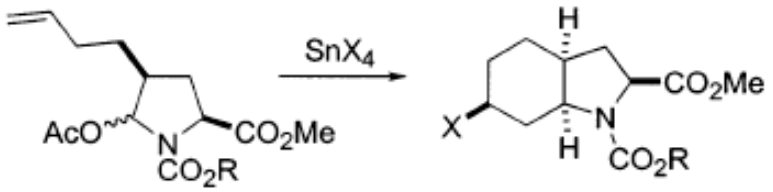
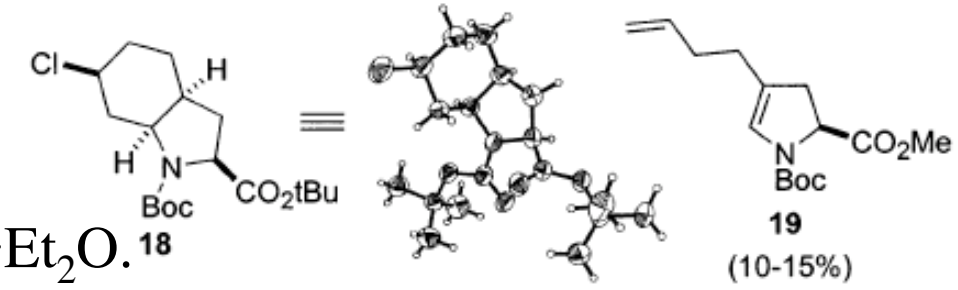
Influence of N-Carbamoyl Group and Lewis Acid for halo-carbocyclization

Hanessian, Stephen, et. al.
J. Am. Chem. Soc. **2004**,
126, 6064-6071

Scheme 3. Variation of the Lewis Acid and *N*-carbamoyl Group in The Formation of the Octahydroindole Cores

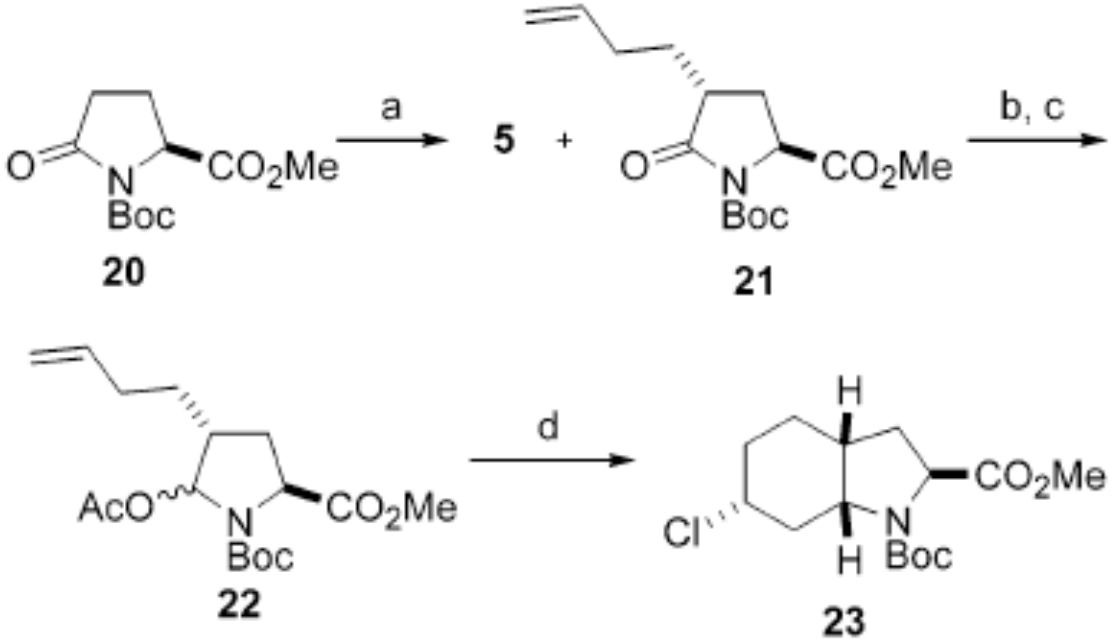


6a-e	7a-e
a R= t-Bu; X= Cl	66%
b R= Bn; X= Cl	60%
c R= Bn; X= Br	61%
d R= Me; X= Cl	66%
e R= Me; X= Br	72%

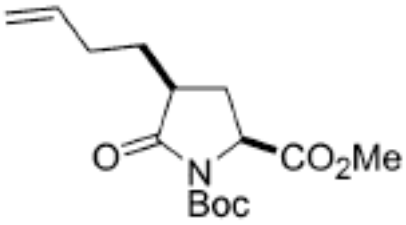


-N-Carbamoyl group had little effect
-Concentrations of 6 from 0.01 to 0.2 M did not effect the yields.
-The Enecarbamate yield increased with use of $SbCl_5$, TMSCl, and $BF_3{\cdot}Et_2O$.
-$ZnCl_2$ resulted in no reaction.
-$TiCl_4$ resulted in complex mixture.
-The reaction was complete in few minutes at -78 C with $SnBr_4$ and $SnCl_4$.
-$SnBr_4$ slightly superior to $SnCl_4$

Epimeric Example



[a]a: LiHMDS, THF, −78 °C, then 3-butenol triflate, 70% (1:1.8 anti/syn); b: $LiHBEt_3$, THF, −78 °C; c: Ac_2O, Et_3N, DMAP, CH_2Cl_2, 87% (two steps); d: $SnCl_4$, CH_2Cl_2, −78 °C, 64%.



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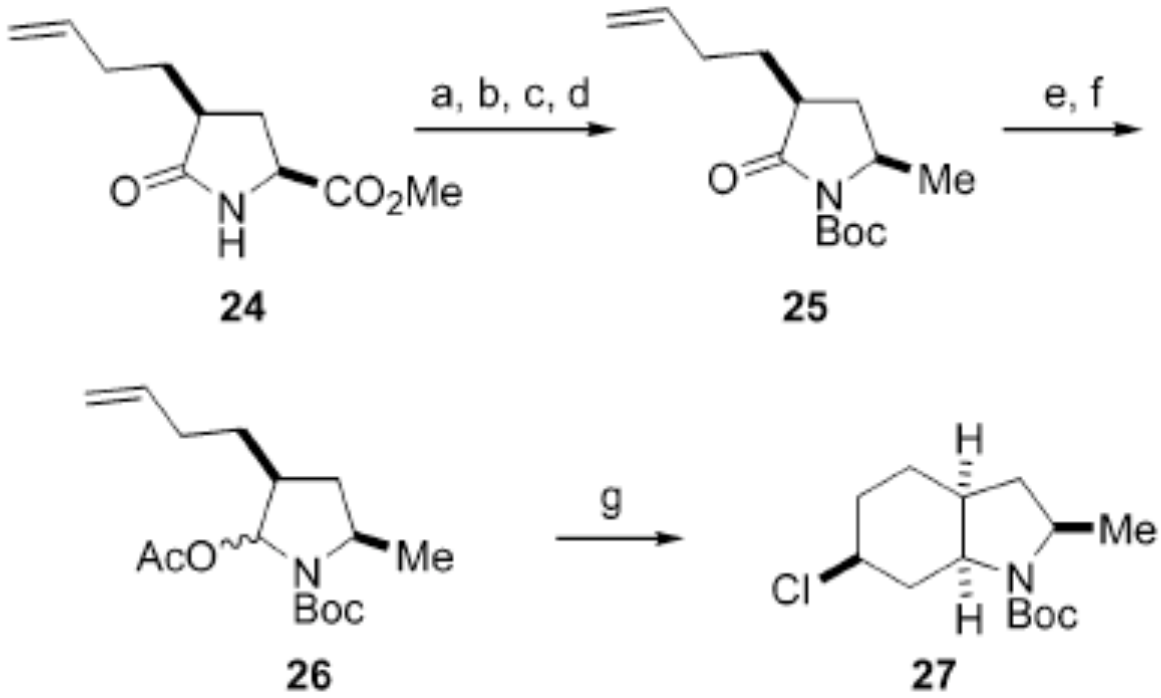
C-Me example



+ 12% enecarbamate

[a] a: $NaBH_4$, EtOH, 87%; b: CBr_4, PPh_3, cyclohexene, MeCN; c: Bu_3SnH, AIBN, toluene, 80 °C; d: Boc_2O, Et_3N, DMAP, CH_2Cl_2, 35% (three steps); e: $LiBHEt_3$, THF, −78 °C; f: Ac_2O, Et_3N, DMAP,CH_2Cl_2, (80% two steps); g: $SnCl_4$, CH_2Cl_2, −78 °C, 60%.

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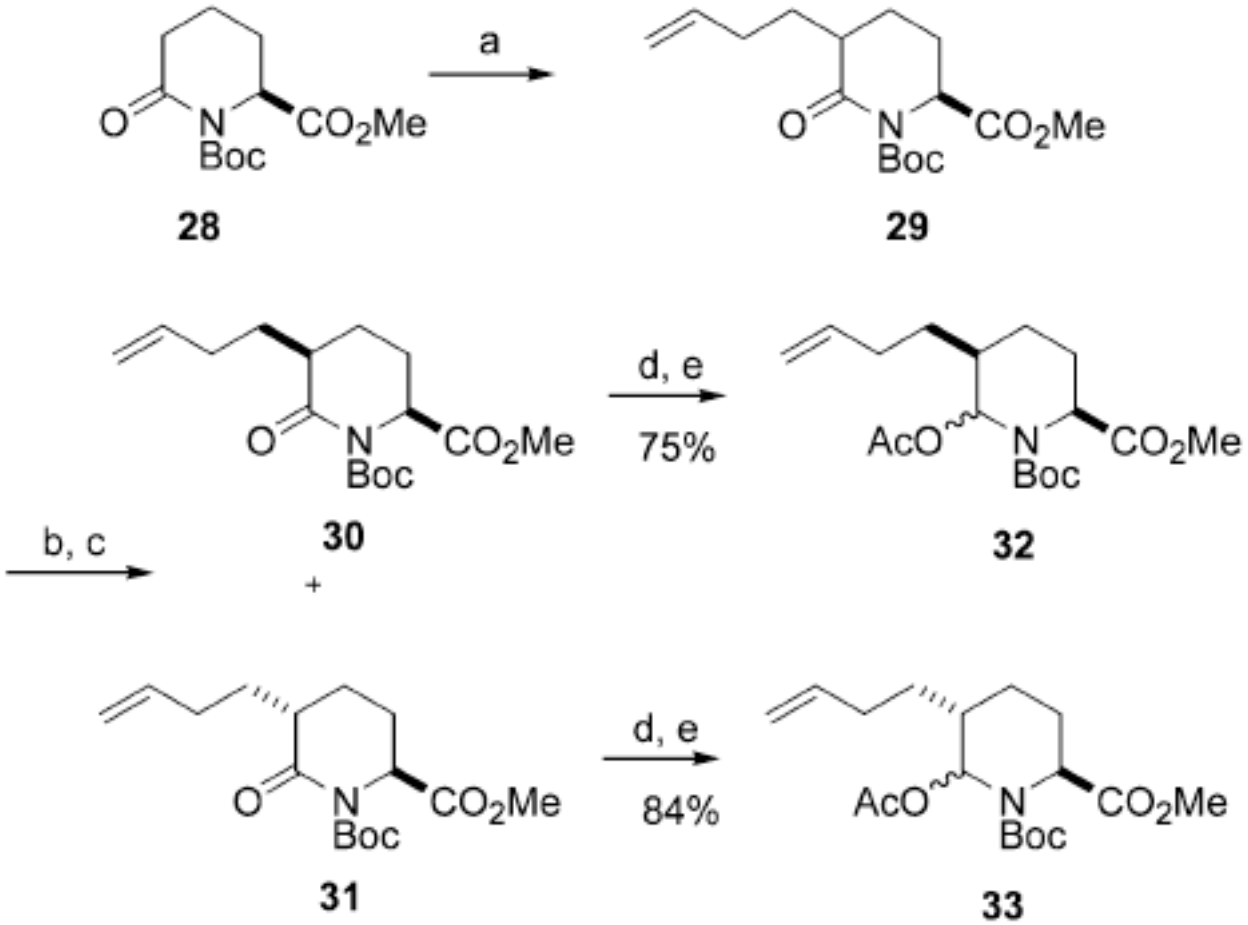
Epimeric Pipecolic Acid Analogues



a: LiHMDS, THF, -78 °C, then 3-butenol triflate, 90% 1.3:1(anti/ syn);
b: TFA, CH2Cl2; c:Boc2O, Et3N, DMAP, CH2Cl2, 78% (two steps);
d: LiBHEt3, THF, -78 °C; e: Ac2O, Et3N, DMAP, CH2Cl2;

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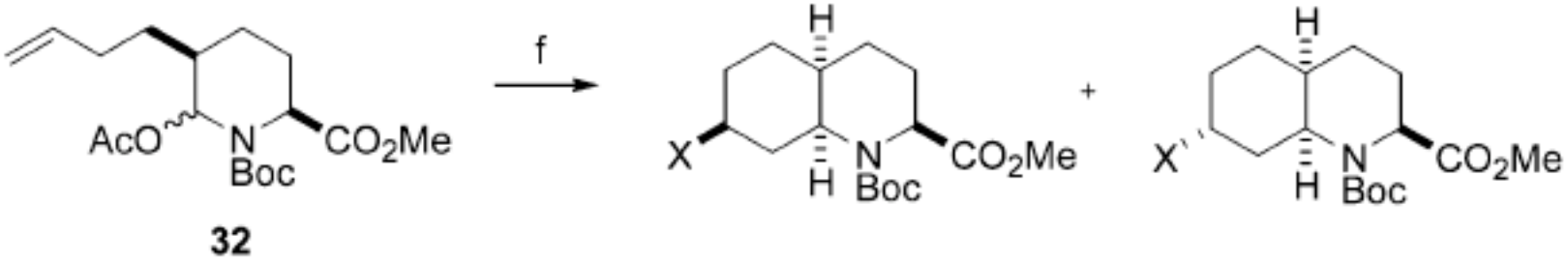
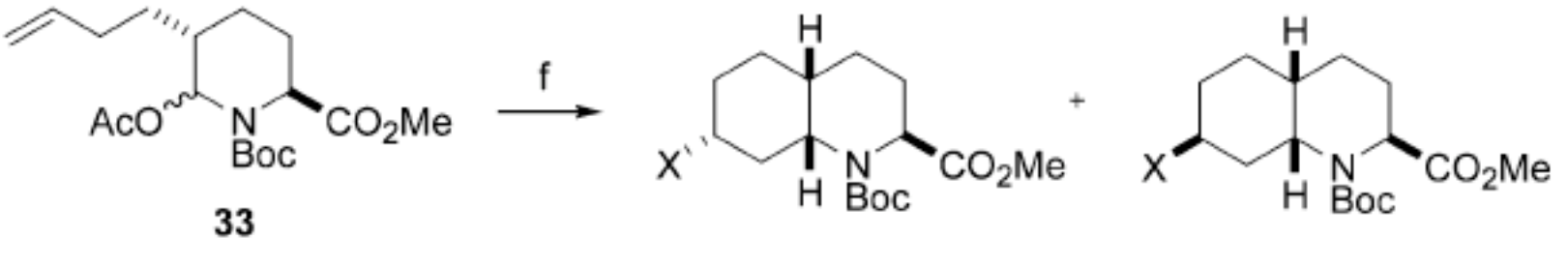
Epimeric Pipecolic Acid Analogues



32

34 X= Cl, 63% (X-ray)
36 X= Br, 65%

35 X= Cl, 8% (X-ray)

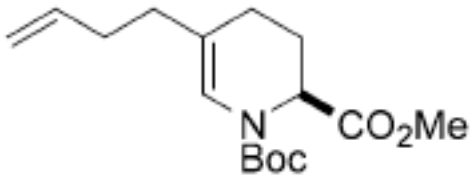


33

37 X= Cl, 35%
39 X= Br, 31%

38 X= Cl, 3% (X-ray)

f: SnX4,CH2Cl2, -78 °C.



40 (30-35%)

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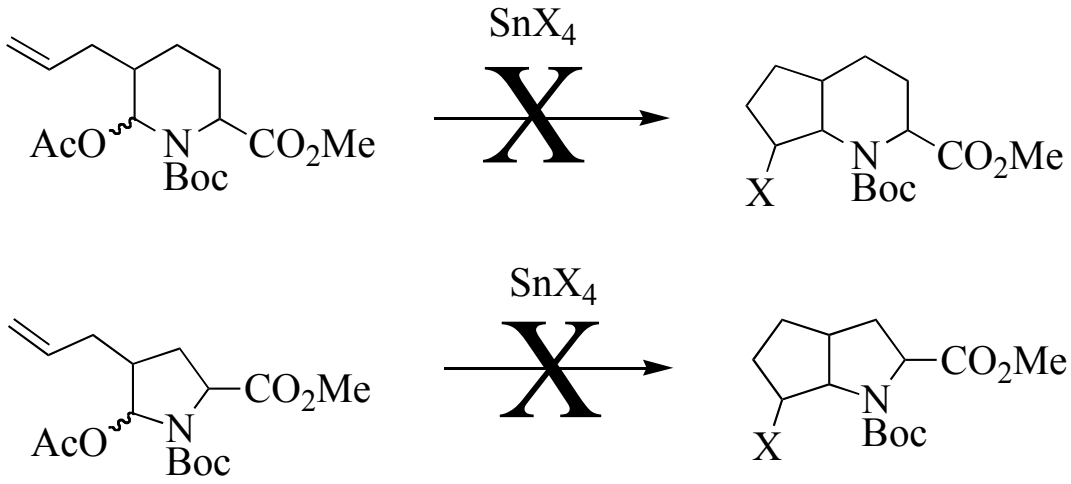
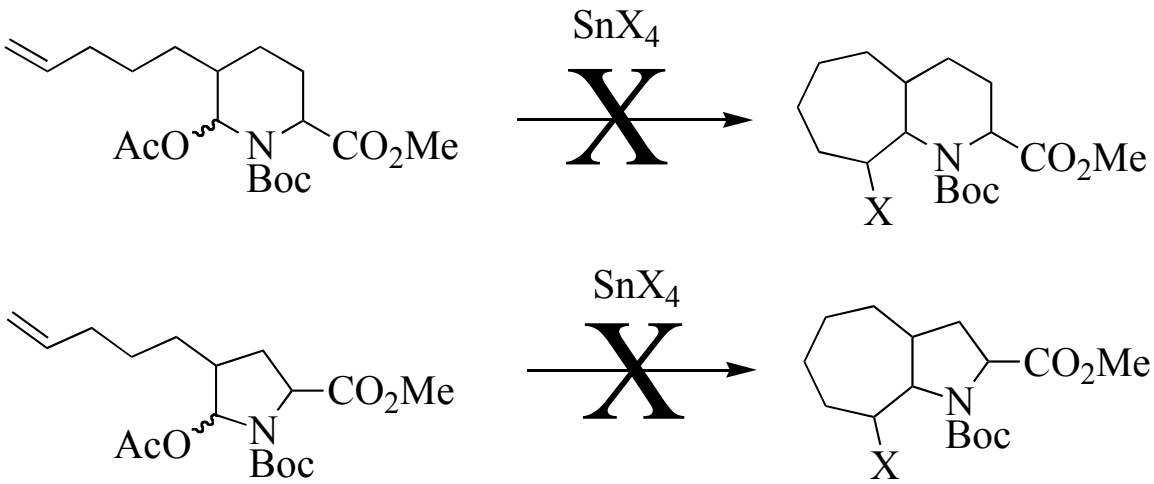
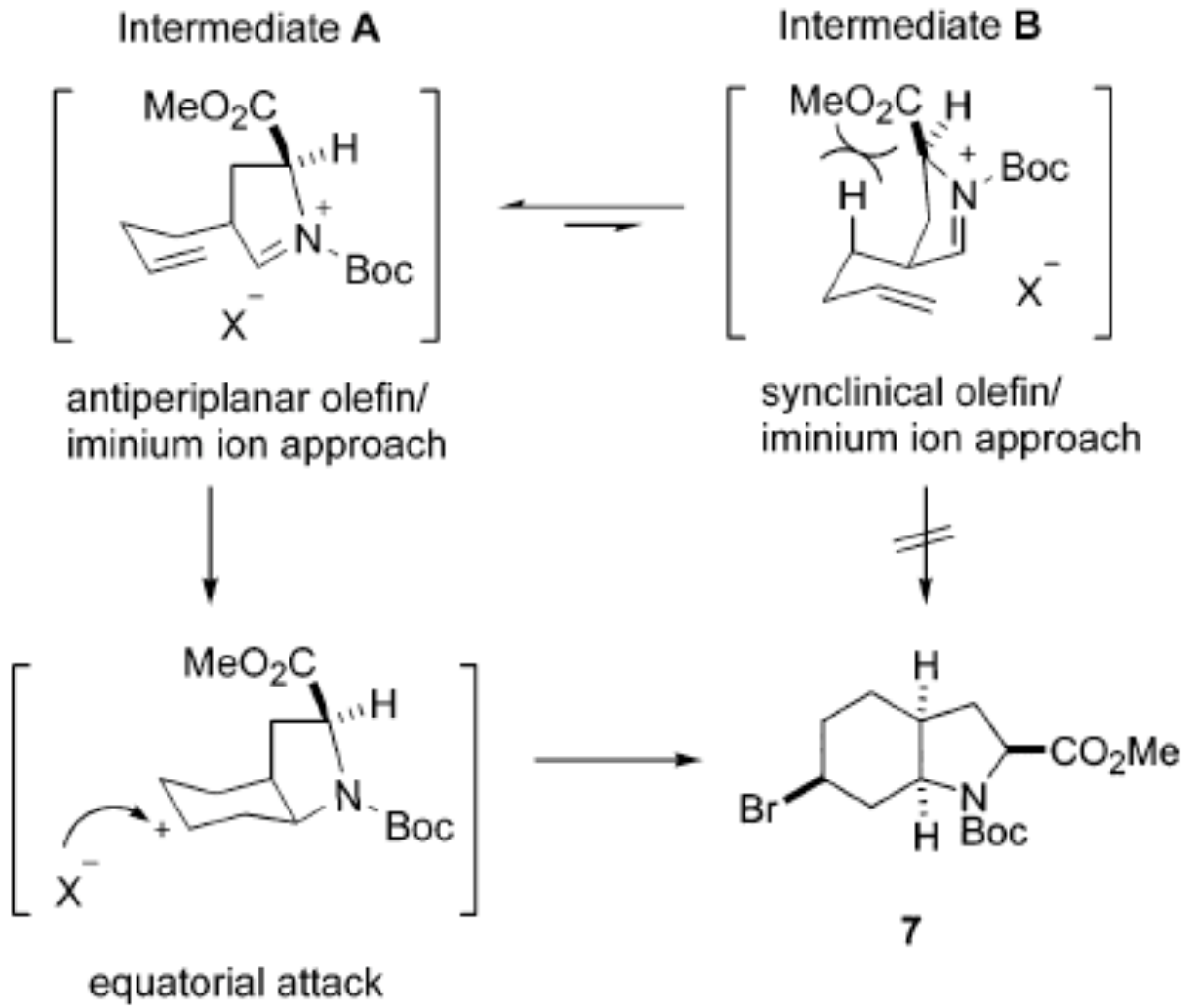
Effect of Tether Length





Proposed Reactive Intermediates Toward Octahydroindoles



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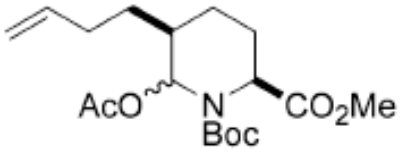
"It is generally agreed that maintaining maximum orbital overlap of the alkenyl π systgems with the developing lone pair on the nitrogen in five- and six-membered N-acyloxyiminium ions is an important requirement."

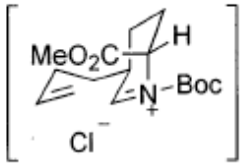
Figure 4. Proposed reactive intermediates in the *N*-acyloxyiminiumion aza-Prins halocarbocyclization to octahydroindoles.

Proposed Reactive Intermediates Toward Perhydroquinolines

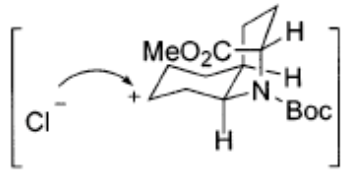


32

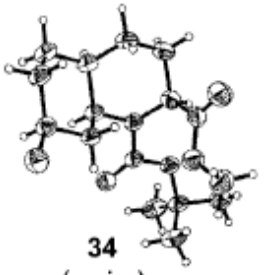
A



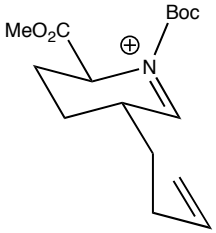
antiperiplanar axial olefin/
iminium approach



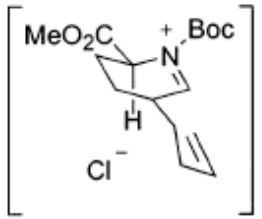
equatorial halide attack



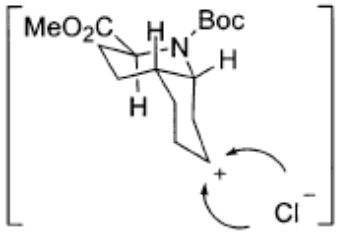
34
(major)



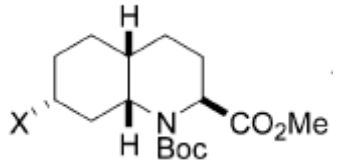
B



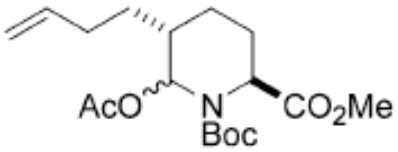
antiperiplanar axial olefin/
iminium approach
$A^{1,2}$ strain (?)



equatorial
attack



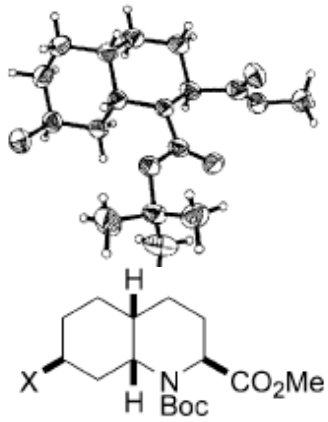
37 X= Cl, 35%



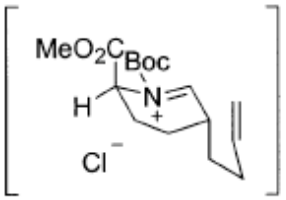
33

C

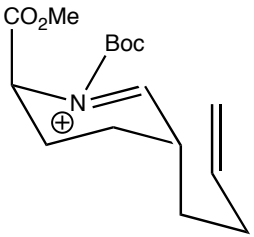
axial
attack

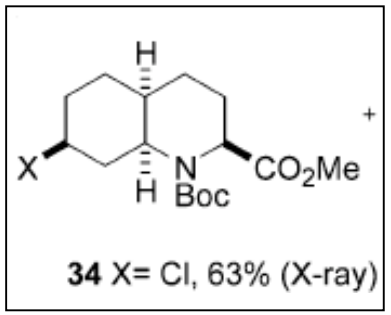


38 X= Cl, 3% (X-ray)



synclinical equatorial olefin/
iminium approach
(not favored ?)

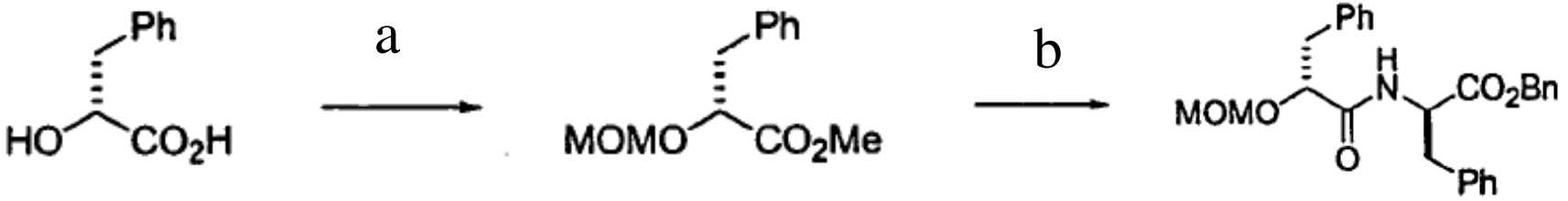




34 X= Cl, 63% (X-ray)

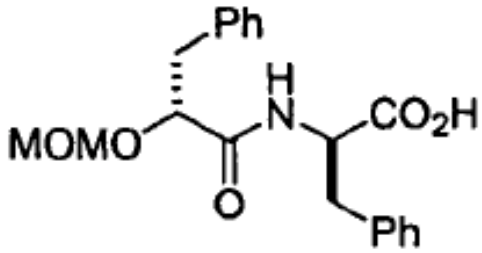

THANKS

Synthesis of **9**



c

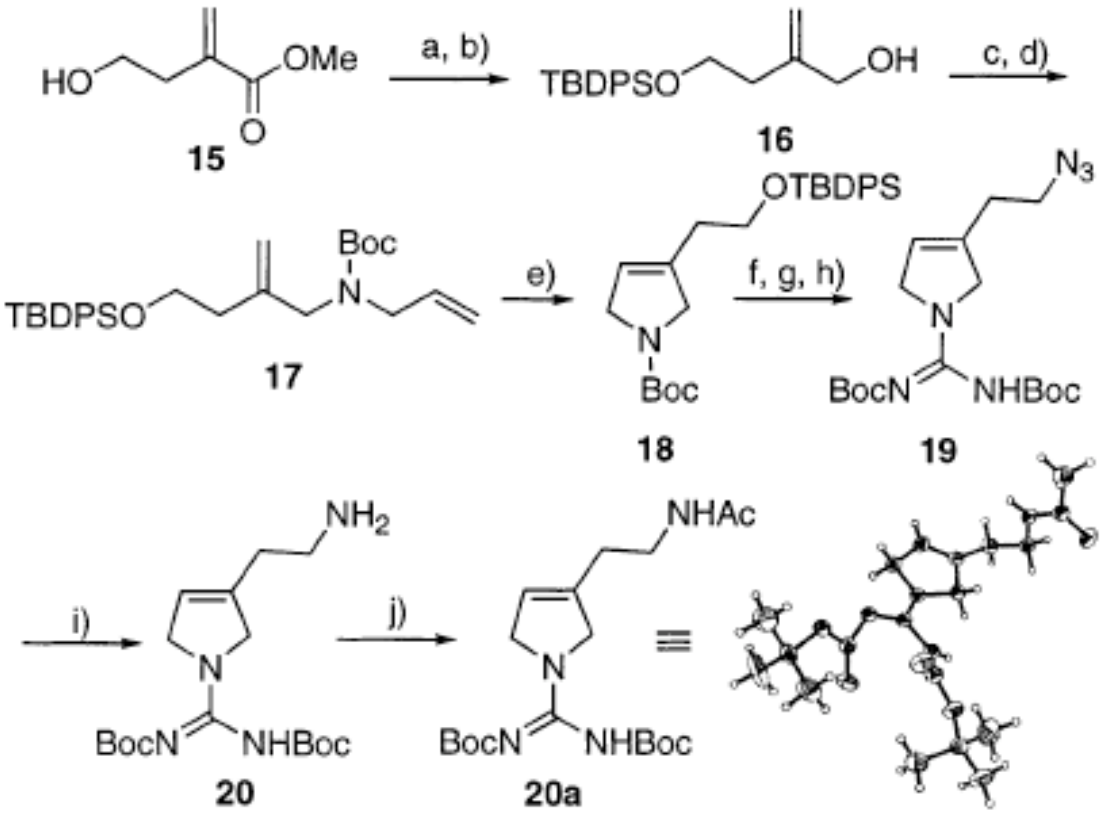
a. 1. CH_2N_2, Et_2O, 2. iPr_2NEt, MOMCl (90%)
b. 1. LiOH then 2N HCl 2. EDC, HOBt, then D-Phe-OBn (89%)
c. H_2, Pd/C (78%)



9

Hanessian, Stephen, et. al. *J. Am. Chem. Soc.* **2004**, 126, 6064-6071

Synthesis of **11**



[a] Reagents and conditions: (a) TBDPSCl, imidazole, DMF; 90%. (b) DIBAL-H,CH_2Cl_2; 90%. (c) MsCl, Et_3N, CH_2Cl_2; then allylamine; 84%. (d) Boc_2O, Et_3N, CH_2Cl_2; quant. (e) Ru benzylidene$(Cy_3P)_2Cl_2$ 10 mol %, CH_2Cl_2; 90%. (f) TBAF, THF; 92%. (g) PPh_3, DEAD, $(PhO)_2P(O)N_3$, THF; 82%. (h) TFA, CH_2Cl_2; then Et_3N, Goodman's reagent; 86%. (i) PPh_3, H_2O, THF then AcOH; 72%. (j) Ac_2O, Et_3N, MeOH; 90%.

Hanessian, et al.; JACS 2002, 13343